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Original Communications

THE HYPOTENSIVE STATE FOLLOWING ACUTE MYOCARDIAL INFARCTION. I.

CLINICAL OBSERVATIONS

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ACUTE myocardial infarction is frequently accompanied or followed by a shocklike state in which the patient appears pale and anxious, the skin is moist and clammy, the pulse rapid and thready, and the blood pressure low or unobtainable. The pathogenesis of this hypotensive state has never been clearly established. Early studies, particularly those by Fishberg and associates[1] were interpreted as pointing to a peripheral mechanism of the hypotensive state, namely, a form of vasomotor collapse leading to a diminished venous return. It was even believed that such a pooling of blood away from the heart may have a beneficial effect upon the circulation in the acutely failing heart, damaged by myocardial infarction.[1] Later, opposing views were expressed by Harrison,[2] Stead and Ebert,[3] and Boyer[4] who considered the hypotensive state as evidence of "forward failure" of the heart as a pump. To emphasize the central mechanism the term "cardiogenic shock" was coined.[4]

In the last few years this controversy has been sidetracked by the observations that the fall of blood pressure to shock levels has a profoundly adverse effect upon the myocardial function[5] and accentuates the damage to the myocardium done by coronary occlusion.[6] In efforts to counteract this damaging effect of the falling blood pressure upon the freshly infarcted heart, plasma and blood infusions were used following acute myocardial infarction with variable results.[7]

A rational therapeutic approach should be based on a knowledge of the mechanism of the physiologic disturbance to be corrected. Therefore, it appears advisable to reopen the problem of the pathogenesis of the hypotensive state associated with acute myocardial infarction. This communication deals with an

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attempt to analyze the clinical features of those patients with acute myocardial infarction who appeared to be in "shock" in the hope of gathering insight into the factors initiating the hypotensive state and to correlate clinical observations with the results of experimental studies to be reported in the following communication.

MATERIAL

The material used for this study consisted of a series of 528 unselected cases of acute myocardial infarction from the files of the San Francisco Hospital. Only those cases were included in which the clinical and electrocardiographic evidence permitted an unequivocal diagnosis of myocardial infarction. The following signs and symptoms of the shocklike state were searched for: hypotension (systolic blood pressure reading below 90 mm. Hg, or correspondingly higher levels in patients with previous hypertension); pallor with ashen cyanosis; perspiration with clammy skin; thready pulse; restlessness, stupor, or coma. Patients in shock were classified as suffering from mild, moderate, and severe shock. Other factors pertaining to the state and efficiency of the heart and circulation were carefully evaluated. Special attention was paid to the clinical pattern of the hypotensive state, its mode of onset, reversibility, duration, and its effect upon the outcome of the disease.

FINDINGS

The incidence of shock and the mortality of patients with and without shock are presented in Table I. It is seen that the mortality of patients who were in shock is more than twice that of patients without shock.

TABLE I. DEATH RATE FROM ACUTE MYOCARDIAL INFARCTION WITH AND WITHOUT "SHOCK"

	NO. CASES	NO. DIED	PER CENT
Total series	528	182	34.5
Patients in shock	69 (13 %)	48	70
Patients without shock	459 (87 %)	134	29

An analysis of the course and clinical features of the sixty-nine cases with shock revealed that they could be divided into four classes: Type I, early shock with recovery; Type II, early shock, persistent, with fatal outcome; Type III, shock associated with cardiac arrhythmias, and Type IV, late shock with a gradual onset.

The incidence of cases in each of the four groups of the shocklike state is presented in Table II, which also contains information pertaining to mortality and the presence or absence of pre-existing cardiac disease.

Group I.—There were twenty-four patients in whom the shocklike state developed immediately after the onset of the initial attack of pain. The characteristic picture of circulatory collapse, with cold perspiration, clammy skin, ashen color with a cyanotic tinge, rapid and thready pulse are familiar as frequently associated with an acute coronary occlusion. In this group of cases, however,

the signs of circulatory collapse cleared promptly either spontaneously, or in response to treatment of the initial attack of pain (morphine, oxygen, etc.). The duration of the shocklike state varied from two to twenty-four hours. In fifteen cases the duration was less than fifteen hours. The level of the systolic blood pressure varied from 125 to 60 mm. Hg. In one-half of the patients the cardiac rate was over 100 beats per minute. Dyspnea was more often absent than present; it was noted in nine patients of whom four had severe dyspnea with pulmonary edema. In the majority of patients the attack was initiated by severe chest pain, but in four patients the pain was described as mild, and in one it was entirely absent. Pre-existing known cardiac disease was more often absent than present (Table II). It is noted that in Table II three patients died but were included in Group I. These were patients in which the initial circulatory collapse cleared, but later in the course of the disease developed late "shock." These therefore constitute duplications and account for the fact that the total number adds to seventy-two instead of sixty-nine.

TABLE II. INCIDENCE OF KNOWN PRE-EXISTING CARDIAC DISEASE AND DEATH RATE IN FOUR TYPES OF SHOCKLIKE STATE FOLLOWING ACUTE MYOCARDIAL INFARCTION

	NO. CASES	NO. PREVIOUS CARDIAC DISEASE	NO. PREVIOUS MYOCARDIAL INFARCTION	NO. PREVIOUS HYPERTENSION	NO. DIED
Group 1	24 (21)	19	3	2	3
Group 2	28	13	7	8	28
Group 3	9	4	3	2	9
Group 4	11	3	1	7	11
Total	72 (69)	39	14	19	48

The following case can be considered a representative example of the shocklike state, Type I.

A 57-year-old man had always been in good health until he awoke one night with a "tight feeling" in the epigastrium, radiating to both shoulders, associated with dyspnea. A physician who was called told him that his condition was satisfactory and that his blood pressure was "140." The following night he awoke with a similar attack, somewhat more severe. He spent the next day in bed and was free from symptoms. During the third night the pain recurred with much greater intensity; the patient collapsed and was brought to the hospital unconscious. Upon admission to the hospital he was found to be in profound shock; his blood pressure was unobtainable, the skin was clammy, ashen cyanosis was evident, and the patient was stuporous and nonresponsive. No dyspnea or orthopnea was noted, but pulmonary râles were heard posteriorly. Heart sounds were distant, and the rate was rapid. The patient was given 0.015 Gm. of morphine and oxygen was administered. Within one hour his pressure was recorded as 70/30 mm. Hg, with a cardiac rate of 96 per minute. The patient remained in the shocklike state for twelve hours, during which time he was anuric; the systolic blood pressure remained below 80 mm. Hg. Gradually, however, the patient became responsive, the blood pressure rose to 95/60 mm. Hg, and the clinical signs of shock disappeared.

On the second day following admission, the patient was comfortable, his blood pressure stabilized at about 100/65 mm. Hg, and the heart rate was about 80 per minute. Electrocardio-

graphic examination revealed an extensive anterior myocardial infarction. The usual signs, fever, leukocytosis, and increased sedimentation rate appeared during the first week after the onset. The patient remained asymptomatic and made an uneventful recovery.

Group II.—There were twenty-eight patients in this group, who developed initially signs of circulatory collapse identical with those of Group I, but in contrast to the latter cases persisted in shock until death. The duration of the shocklike state varied from four hours to six days. In ten patients death occurred in less than twelve hours; in sixteen in less than twenty-four hours. In the remaining twelve patients a continuous shocklike state persisted for over twenty-four hours, in three of them for more than two days. The blood pressure was unobtainable in eight patients, was recorded as between 40 and 95 mm. Hg systolic in fifteen and was over 100 mm. Hg in five. The heart rate was recorded in twenty-five patients and was under 100 beats per minute in eight, over 100 in seventeen. Dyspnea was present in eighteen cases and was absent in ten. The initial attack of pain was almost always recorded as severe, often described as extreme, excruciating. It was reported as mild in only two cases and in one it was absent. The incidence of pre-existing cardiac disease is shown again in Table II. It is seen that it was present in about one-half of the patients.

A typical case of early hypotensive state leading to a fatal outcome is summarized below.

A 65-year-old man had a typical attack of coronary occlusion in 1937, from which he recovered uneventfully except for mild exertional angina of effort. This did not progress until eight years later, November, 1945. At that time his tolerance for effort became gradually more limited because of chest pain. On Nov. 30, 1945, he developed a crushing substernal pain, associated with cold perspiration and apprehension, which was not relieved by nitroglycerin. One hour after the onset of the pain he appeared in moderate shock. His blood pressure fell from 165/90 to 105/60 mm. Hg. The heart rate was 88 per minute; there was some dyspnea and a few pulmonary râles were noted. The following morning the patient still appeared in a shocklike state; he was restless, stuporous, and irrational. Cheyne-Stokes respiration was noted. Blood pressure persisted at a level of 85/55 to 90/60 mm. Hg. Heart rate was about 120 per minute. An electrocardiogram showed an extensive anterior myocardial infarction. There was an elevation of temperature of between 38 and 39° C.; there was a leukocytosis of 21,000 cells per c.mm. The patient persisted in the shocklike state for eight days. On the sixth day early gangrene of the fingertips and some discoloration of the tip of the nose was noted. He died quietly on the eighth day. Autopsy revealed an old myocardial infarction in the posterior wall of the left ventricle, a total occlusion of the right coronary artery by a thrombus, and massive myocardial infarction of the anterior wall of the left ventricle and the septum.

Group III.—In nine patients the hypotensive state coincided with a disturbance of cardiac rhythm. In seven patients bradycardia was noted, namely, complete atrioventricular block in five and nodal bradycardia in two. Paroxysmal ventricular tachycardia was recorded in two. The duration of the "shock" was less than twenty-four hours in eight patients, while two patients survived the hypotensive state associated with complete heart block for three days. The systolic blood pressure was below 100 mm. Hg in all patients; in two it was recorded as "unobtainable." Dyspnea was reported as present in six patients.

The following case illustrates this type of "shock."

A 64-year-old man entered the hospital on Dec. 6, 1947, for treatment of urinary tract obstruction. While under treatment, on December 10 he was suddenly seized by a severe, nonradiating substernal pain following which he developed dyspnea and prostration. He was known to have mild arterial hypertension with cardiac enlargement and mild left ventricular failure which was controlled by digitalis. The blood pressure recorded on admission was 160/100 mm. Hg, falling to 135/80 after the attack. An apical gallop rhythm was heard, the heart rate was 80 per minute, rhythm regular, and the circulation time (arm-to-tongue) was 27 seconds. A mild leukocytosis and fever developed, and the electrocardiogram showed a left bundle branch block. Clinical progress was apparently satisfactory until December 12 when, at 8:00 A.M., the patient suddenly developed orthopnea, labored breathing, and severe apprehension. His heart rate was found to be 200 and the rhythm was regular. An electrocardiogram revealed ventricular tachycardia. His blood pressure was found to be 130/105 mm. Hg at first, but an hour later was 85/70 mm. Hg. He developed restlessness, ashen cyanosis, cold and clammy skin. The shocklike state gradually deepened, the tachycardia persisted in spite of attempts to terminate it, and the patient died four hours after the onset of the attack of arrhythmia.

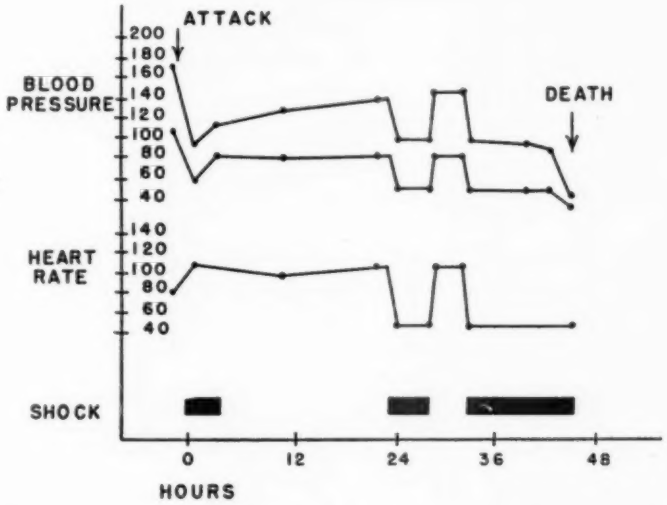

Fig. 1.—Graphic presentation of the course of the illustrative case of shock, Types I and III.

The following case exemplifies a combination of Type I and Type III of "shock."

A 62-year-old man entered the hospital one hour after the onset of severe substernal pain radiating to both arms and both sides of the neck (Fig. 1). He was well prior to the attack except for attacks of substernal pain on exertion for the preceding two weeks and several attacks of pain at rest in the preceding forty-eight hours. The attack of chest pain was associated with nausea and repeated vomiting. On admission to the hospital the patient appeared pale and anxious, perspiration was profuse, and the skin clammy. He was very restless even after two injections of 0.015 Gm. morphine. His blood pressure which was known to be 160/100 mm. Hg prior to the attack was recorded as 90/60 mm. Hg.

The patient was placed in an oxygen tent and within three hours the pain subsided, the signs of shock disappeared, and the blood pressure rose to 110/80 mm. Hg. The following morning he was comfortable and his condition was considered satisfactory. There was moderate leukocytosis, the temperature was elevated to 39.0° C., and the electrocardiogram revealed the pattern of posterolateral myocardial infarction.

Twenty-four hours following admission there was a sudden change in the patient's condition; restlessness and confusion reappeared and signs of shock became apparent again. The heart rate was found to be 40 per minute, with an electrocardiographic tracing showing complete atrioventricular block. The blood pressure, which a few hours previously was 125/80 mm. Hg, fell to 90/60 mm. Hg. Four hours later there was again improvement in the patient's condition which coincided with a return of heart rate to 90 per minute. However, after a few hours, heart block reappeared and the signs of shock deepened, with the patient becoming stuporous and anuric. He persisted in this state in spite of vigorous therapeutic measures which included two units of plasma administered intravenously, and he died forty-eight hours after the onset of the initial attack of pain. Autopsy revealed extensive infarction of the posterior wall of the left ventricle.

Group IV.—This group included eleven patients, all of whom died within forty-eight hours after the onset of the attack of myocardial infarction. Characteristically, the hypotensive state was not present upon admission to the hospital, but developed later, usually several hours to thirty-six hours after the onset. Signs of shock grew progressively worse and there was a gradual fall in blood pressure. The initial attack of pain was of variable intensity. It was described as severe in six cases, mild or moderate in three, and absent in two. Dyspnea was present in all cases, and was severe in most of them. The cardiac rate was over 100 per minute in all but two cases.

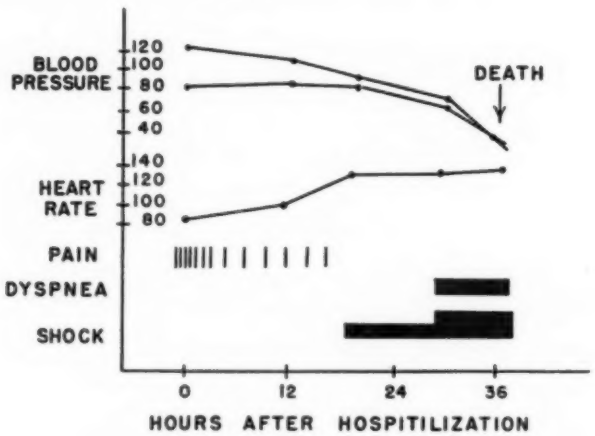

Fig. 2.—Graphic presentation of the course of the illustrative case of shock, Type IV.

The following case presents a typical picture of shocklike state of the pattern described.

A 54-year-old man, who had had an attack of coronary occlusion four years previously, developed suddenly severe substernal pain which was intermittent, in that it appeared in attacks of about ten minutes' duration, twenty to thirty minutes apart (Fig. 2). He was hospitalized and upon admission to the hospital his condition was considered satisfactory. His blood pressure was 120/80 mm. Hg, heart rate 80 per minute, and there were no abnormal findings on physical examination. While in the hospital the attacks of pain kept on recurring but with somewhat lesser intensity. Fifteen hours after the onset, the blood pressure was 105/85 mm. Hg, and the heart rate 100. Nausea and prostration appeared. That evening (a few hours later) the pain was less severe, but the heart rate rose to 136 per minute, the blood pressure fell to 92/80 mm. Hg, and the patient presented for the first time signs of the shocklike state. Dyspnea also became apparent with some cyanosis. The following morning signs of shock deepened. The patient was semi-

comatose, orthopneic, the blood pressure 75/65 mm. Hg, and the heart rate 120 per minute. A few hours later the patient was pulseless, the blood pressure unobtainable, and cyanosis more intense. Death occurred about forty hours after the onset of the attack. Autopsy revealed a massive myocardial infarction involving a large part of the left ventricle, due to occlusion of the left anterior branch of the coronary artery.

DISCUSSION

The problem of shock is one of great complexity. The many factors participating in the shock syndrome can be divided into those initiating shock, those maintaining the state of shock, and those responsible for the clinical manifestations and sequelae of shock. The more important factors are summarized in Fig. 3, where an attempt is made to stress and separate the primary, "initiating" factors from the secondary, "sustaining" factors, and to point out the vicious cycle associated with the persistence of the shock and shocklike state. It is seen that the actual cause of the clinical syndrome known as shock is, regardless of cause and origin, an abrupt fall in the left ventricular output. Factors leading to

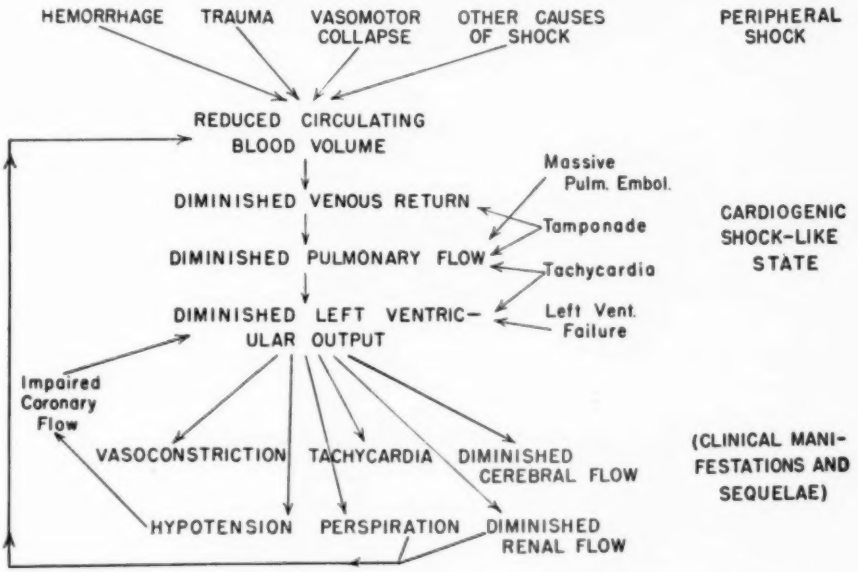

Fig. 3.—Interrelationship of factors initiating and sustaining various forms of shock and the various clinical manifestations.

this reduction of output fall into two categories: those causing a reduction of the venous return, and those acting upon the various segments of the heart and the pulmonary circulation. The first group includes all forms of shock and collapse of "peripheral" origin, and the second one the "central" or "cardiogenic" forms of the shocklike state. This division applies, of course, only to the primary, initiating factor. Once present, shock and the shocklike state alike set up identical vicious cycles, maintaining the hypotensive state and bringing into the picture central factors in shock of peripheral origin, and peripheral factors in cardiogenic forms. Some of these vicious cycles are shown in the diagram by the arrows on the left side of the chart.

The hypotensive state following acute myocardial infarction could be, theoretically, initiated by either mechanism. The clinical manifestations would be identical regardless of whether it was initiated by a peripheral or by a cardiac mechanism. It is obvious, therefore, that once the state of shock develops and the vicious cycles start operating, the determination of the initiating mechanism may well be impossible. It is believed, therefore, that clinical observation as to the mode of development of the hypotensive state and the clinical pattern could provide more information in that respect than more exact studies of the circulation, the blood volume, and the electrolyte response.

In this series, the most important group providing a clue as to the mechanism of the hypotensive state is Group III. In it, the clinical picture of shock coincided with the presence of a disturbance of cardiac rhythm. The relationship between the extreme range of cardiac rate and the shocklike state has been such that coincidence can be safely ruled out. In almost every case did the two appear at the same time and in two cases with complete heart block the bradycardia appeared intermittently and the clinical manifestations of shock were noted only at the time while it was present, while the patient was out of shock each time the normal rate was resumed. Furthermore, it is well known that severe tachycardia may bring about a shocklike state even in the presence of a normal circulation,[8] while extreme tachycardia may bring about cardiac syncope.[9] Heart block, on the other hand, does not ordinarily lead to important symptoms at rest until bradycardia reaches a critical level causing cardiac syncope. At both extremes of the range of cardiac rate, the output falls. It appears that this fall of cardiac output superimposed upon the already inadequate circulation maintained by an infarcted myocardium may bring about the shocklike state. The suggested clinical manifestations of extreme ranges of cardiac rate with and without myocardial infarction are presented in Table III.

TABLE III. POSSIBLE CLINICAL MANIFESTATIONS ASSOCIATED WITH EXTREME RANGES OF CARDIAC RATE, WITH AND WITHOUT MYOCARDIAL INFARCTION

	DEGREE	CLINICAL MANIFESTATION WITH	
		NORMAL CIRCULATION	IMPAIRED CIRCULATION (MYOCARDIAL INFARCT)
Bradycardia	Moderate	None	Shocklike state
	Extreme	Syncope	Syncope
Tachycardia	Moderate	None	Shocklike state
	Severe	Shocklike state	Shocklike state or syncope
	Extreme	Syncope	?

Patients separated in this series as Group IV showed a clinical pattern characterized by the late onset of the hypotensive state and a gradual, relentless downhill course with fatal termination in each case. This pattern shows a definite resemblance to cardiogenic shock produced experimentally.[10] It is exceedingly

likely that this late "shock" is a clinical manifestation of progressive failure of the infarcted left ventricle. Dyspnea was observed in all cases in this group.

The immediate development of the shocklike state following the initial attack of pain is represented by cases of Groups I and II. This clinical pattern stands out in a striking contrast with those in Groups III and IV. The pattern of the Groups I and II was identical, and the division was made arbitrarily on the basis of the outcome, presenting a purely quantitative difference. The sudden, precipitous fall in blood pressure coinciding with the attack of pain strongly suggests the possibility that the shocklike state was initiated by a neurogenic reflex mechanism, or some other peripheral mechanism affecting the venous return, and secondarily reducing the cardiac output. A peripheral mechanism initiating shock explains the reversibility of milder instances of early shock, which would hardly be probable if it was caused by cardiac failure. Furthermore, the recovery from this shocklike state was either spontaneous, or in response to simple measures, such as bed rest, relief of pain with no therapeutic efforts directed towards strengthening of the myocardium. In fatal cases (Group II), the persistence of the shocklike state must have been aided by the serious sequelae of prolonged hypotension upon the coronary circulation to the uninfarcted myocardium and the contraction of the ischemic myocardium.[6] In those cases cardiac failure undoubtedly was a factor in sustaining the shocklike state. It is noteworthy that dyspnea was frequently absent in patients in Groups I and II. Even in some cases where the patients persisted in the shocklike state for days, the absence of the respiratory distress and orthopnea often stood out in striking contrast to the average patient in cardiac failure.

Among patients in Group II, there were a few in whom the onset of pain was followed by immediate development of the shocklike state in its most dramatic form with death ensuing within a few hours. Some of these were shown at autopsy to have very extensive infarcts of the myocardium. In those cases, both central and peripheral factors may have been operative from the onset summing up into a complete breakdown of the circulation.

It has been suggested in the foregoing discussion that the two initiating factors of the shocklike state, the peripheral vasomotor collapse and the acute left ventricular failure, both play an important part in the clinical picture of the hypotensive state. While both factors are unquestionably playing some part in each case, early shock is believed to be caused predominantly by a peripheral mechanism, while late shock and that associated with the extremes of the range of cardiac rate are probably central in origin. In suggesting that early and late shock are due to an entirely different mechanism, one should point out that a somewhat analogous situation exists in other forms of shock. The early circulatory collapse due to trauma, surgical operation, spinal anesthesia, or cerebral injury is of entirely different origin than the late, true ("secondary") shock which can develop following these conditions. Furthermore, a reflex vasomotor collapse may be precipitated by various vascular accidents associated with pain, such as embolic occlusion of mesenteric or femoral arteries, and there appears to be no reason why coronary occlusion should not on occasion cause such a complication. The actual stimulus for the reflex vasomotor paralysis in early shock is not known.

Pain may be an important factor, although it certainly is not the only one. Occasionally shock may appear in the absence of pain, as it occurred in one of our cases. It is well known that a sudden collapse may be the only manifestation of a painless myocardial infarction.

The initiating mechanism of the hypotensive state of acute myocardial infarction is of more than academic interest. Prolonged hypotension following myocardial infarction may cause such serious consequences to the myocardium and its function that one could well think in terms of attempting to maintain a reasonable blood pressure level at all costs. Yet, therapeutic measures designed to combat vasomotor paralysis and depleted circulating blood volume appear to be contraindicated in acute cardiac failure, and vice versa. In the first case one thinks in terms of blood and plasma infusion and pressor amines,[7,11] while in the other case venesection and stimulation of the uninfarcted myocardium would appear to be more indicated.[4] Both blood transfusion and venesections have been performed in acute myocardial infarction. Neither of these procedures has proven to be of definite benefit, nor has either been shown to be harmful. The difficulty in evaluating the efficacy of such procedures is obvious because of the precarious condition of the patients and the unpredictable outcome.

Neither the clinical observations presented in this communication, nor the experimental studies reported in the following paper,[13] permit the establishment of therapeutic criteria for the management of the hypotensive state following acute myocardial infarction. Until the exact nature of the initiating factors responsible for this disturbance are uncovered, the theory of treatment will have to be based on speculation and empirical observations. It is felt, however, that the dual origin of the hypotensive state should always be considered in treating patients manifesting the shocklike state.

SUMMARY AND CONCLUSIONS

A series of 528 unselected cases of acute myocardial infarction was examined for the purpose of determining the incidence and the clinical pattern of the shocklike state following coronary occlusion. Sixty-nine patients were found to be suffering from the shocklike state. The mortality rate of those cases was more than twice that of patients without shock.

The cases with manifestations of the shocklike state fell into four categories:

1. Immediate shock, mild form, with precipitous fall in blood pressure.
2. Immediate shock in its severe form with irreversible hypotensive state and fatal termination.
3. Shocklike state coinciding with and apparently due to cardiac arrhythmias with extreme range of the cardiac rate.
4. Delayed development of the shocklike state with gradual fall in blood pressure and invariable fatal outcome with manifestations of cardiac failure.

The pathogenesis of the shocklike state is discussed with special reference to the initiating factors. It is suggested that early shock may be initiated by a peripheral, reflex, vasomotor mechanism, while the late shock (Group IV), may well be a manifestation of irreversible cardiac failure of the "forward failure" type.

The therapeutic possibilities of approaching the problem of the hypotensive state of acute myocardial infarction are discussed in the light of these findings.

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THE HYPOTENSIVE STATE FOLLOWING ACUTE MYOCARDIAL INFARCTION. II.

EXPERIMENTAL STUDIES*

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IN CONTRAST to the extensive investigative work done on experimental electrocardiography of acute myocardial infarction, relatively few studies have been devoted to the dynamics of the circulation following experimental coronary occlusion. It has been shown that the ligation of a major branch of a coronary artery in the experimental animal, which results in acute myocardial infarction, causes transient hypotension following which the circulation is adequately maintained by the uninfarcted myocardium,[1] provided the animal does not succumb to ventricular fibrillation. Evidence for some left ventricular failure has also been demonstrated.[2] However, experimental reproduction of circulatory failure associated with the hypotensive, shocklike state has not been successfully accomplished without invoking such unnatural procedures as severe hemorrhage.[3]

In the light of the controversy as to whether the postinfarction shocklike state is caused by peripheral circulatory collapse or by "forward" failure of the damaged left ventricle, it appeared desirable to make further attempts to reproduce this state in the animal.

METHODS

The study was performed on medium-sized dogs (average 10 kilograms) under pentobarbital anesthesia (30 mg. per kilogram). The experiments were designed to study the immediate effect of acute ligation of one and of two main branches of the coronary arteries upon circulatory dynamics. The performance of the heart was tested by its response to an increased load. In a series of preliminary experiments it was shown that pressure load upon the left ventricle was more dependably reproducible than volume overload. The most satisfactory load stimulus was found to be the brief occlusion of the descending aorta by outside constriction.

The experiments were performed as follows: The chest of the anesthetized dog was opened and artificial respiration instituted with a mechanical respirator

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pump. After opening the pericardium, the area of the heart located between the left auricular appendage and the first portion of the pulmonary artery was carefully dissected accompanied by the liberal use of a 1 per cent solution of procaine. At that point the left coronary artery emerges from the aorta and, within 0.5 and 1.5 cm. from its origin, divides into two or, rarely, three branches. In one or two instances two coronary arteries emerged adjacent to each other directly from the aorta. The two main branches of the left coronary artery were then dissected and a loose ligature was placed around them. The thoracic aorta just distal to the left subclavian artery was then isolated and a tape placed around it. Following this preparation two No. 7 Cournand catheters were placed in both cardiac ventricles under fluoroscopic aid. The one in the right ventricle was introduced through the right jugular vein, the one in the left ventricle through the left carotid artery. These catheters were connected with two Statham strain gauges which were connected to Brush strain analyzers and a two-channel magnetic pen recorder, so that a continuous pressure tracing could be taken from both ventricles. The experiments were divided into two time periods: the control period which usually lasted through the first hour, and the postcoronary-ligation period which extended the following one hour to two hours. In some animals a third period was added, that following the ligation of the second branch of the coronary artery. In some experiments the control period was shortened and in others lengthened in order to eliminate the possibility that the duration of the manipulation may have affected the results of the experiments. In order to produce increased load upon the left ventricle in a standardized manner, total occlusion of the descending thoracic aorta by a Blalock clamp for a period of between thirty and sixty seconds was performed. The duration of the occlusion depended upon the attainment of a satisfactory plateau of the systolic pressure in the left ventricle. This constriction was repeated several times at about ten-minute intervals until consistent results were obtained. Following this control period the larger of the two dissected major branches of the left coronary artery was ligated and a myocardial infarction produced. In most instances the ligated artery was the left descending branch. As soon as the pressure curves became stabilized, which usually occurred within a few minutes, aortic constriction was performed in the same manner as during the control period. The experiments were thus continued for one to two hours, following which time the animal was killed and an autopsy performed. In one-half of the animals, approximately one hour after the ligation of the first branch of the coronary artery, the other branch was ligated. In animals which survived this second myocardial infarction aortic constriction was done periodically in the same manner as before. In two animals extensive bleeding was done during the control period and then repeated during the myocardial infarction stage in order to reduce the systolic pressure to shock levels. Following the production of hemorrhagic shock, aortic constriction was performed a few times and the dog was then reinfused. This same procedure was later repeated after production of myocardial infarction.

RESULTS

In preliminary experiments rapid intravenous and intracardiac infusions of saline were tested as to their effect upon intracardiac pressures. The result of such infusions was a mild elevation of intraventricular systolic pressures of the respective chambers and an inconstant slight rise in end-diastolic pressures, the magnitude and duration of which were variable. On the other hand an occlusion of the thoracic aorta produced a sustained and constant elevation of left intraventricular systolic pressure which was found to be well suited for statistical evaluation. The rise in systolic pressure in the left ventricle developed within two beats following the constriction and continued gradually until a plateau was reached, which occurred on the average within ten to fifteen beats. In a few experiments the elevation of the systolic pressure was more gradual and the peak was not reached until twenty to forty beats after the application of the stimulus, but the response of the ventricle was in all other respects identical. The diastolic pressure in the control experiments showed no elevation or a slight gradual rise which reached its maximum within twenty to thirty seconds. Aortic constriction for a period of one minute or less had no visible effect upon pressures in the right ventricle.

The dynamic effects of the ligation of one branch of the coronary artery were variable. A mild fall of the resting level of the systolic pressure in the left ventricle and some elevation of the end-diastolic pressure were frequently, but not invariably, observed. The additional ligation of the second branch of the coronary artery led, on the other hand, to a profound change in circulatory dynamics consisting of systolic hypotension and elevation of the end-diastolic pressure in the left ventricle.

Following the standardization of the technique in the preliminary experiments, the problem was studied on twelve dogs. Seventy-six observations were made. They included twenty-five control experiments, thirty-five observations following the ligation of one branch of the coronary artery, and nine observations following ligation of two branches. In addition, seven observations were made on animals in which bleeding was performed.

The results of the experiments are presented in Tables I and II and in Figs. 1 and 2. They represent the averages, the ranges, and the standard deviation of the responses of pressures in the left ventricle to the increased load of aortic constriction, and the fall in pressures upon the release of the constriction. The readings shown in the tables and figures represent the highest levels obtained during the period of constriction of the aorta and the lowest levels to which the blood pressure fell within the first thirty seconds after the release of the constriction.

It is seen from the tables and the charts that the systolic pressure in the left ventricle showed a rise averaging 57 mm. Hg upon constriction of the aorta, and the fall upon the release of the constriction was of greater magnitude, so that a level lower than the control was reached. This fall in pressure was transient and within two or three minutes previous levels were regained. In some animals this fall in blood pressure was so pronounced that shock levels of systolic pressures

TABLE I. EFFECT OF OBSTRUCTION OF THORACIC AORTA UPON SYSTOLIC AND DIASTOLIC PRESSURES IN LEFT VENTRICLE OF DOGS IN (A) CONTROL ANIMALS, (B) THOSE WITH LIGATION OF ONE BRANCH OF CORONARY ARTERY, AND (C) THOSE WITH LIGATION OF TWO BRANCHES OF CORONARY ARTERY

	CONTROL (25 OBSERVATIONS) (mm. Hg)	LIGATION OF ONE BRANCH (35 OBSERVATIONS) (mm. Hg)	LIGATION OF TWO BRANCHES (9 OBSERVATIONS) (mm. Hg)
Initial level of systolic pressure:			
Mean	115	101	66
Range	62–163	60–137	48–95
Standard deviation	±25.4	±22.5	±14.2
Increase in systolic pressure due to aortic constriction:			
Mean	57	61	11
Range	41–90	35–95	−10–30
Standard deviation	±16.2	±16.8	±12.2
Fall in systolic pressure upon release of obstruction:			
Mean	83	83	22
Range	45–132	55–125	0–30
Standard deviation	±21.5	±17.6	±6.1
Initial level of diastolic pressure:			
Mean	1	10	22
Range	−8–8	8–19	11–32
Standard deviation	±4.5	±4.4	±7.0
Increase in diastolic pressure due to aortic constriction:			
Mean	6	10	10
Range	0–15	5–15	4–22
Standard deviation	±4.3	±3.7	±5.0
Fall in diastolic pressure upon release of constriction:			
Mean	6	8	7
Range	0–11	0–18	3–10
Standard deviation	±3.7	±3.6	±2.2

TABLE II. COMPARISON OF AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES IN LEFT VENTRICLE IN ANIMALS RENDERED HYPOTENSIVE BY BLEEDING WITH THOSE WITH HYPOTENSION DUE TO MASSIVE MYOCARDIAL INFARCTION

	MYOCARDIAL INFARCTION WITH HEMORRHAGIC SHOCK (mm. Hg)	MASSIVE MYOCARDIAL INFARCTION (mm. Hg)
Initial level of systolic pressure	56	66
Increase in systolic pressure due to aortic constriction	66	11
Fall in systolic pressure upon release of constriction	74	22
Initial level of diastolic pressure	9	22
Increase in diastolic pressure due to aortic constriction	5	10
Fall in diastolic pressure upon release of constriction	5	7

were temporarily produced. In a few instances a state of hypotension existed at the beginning of the experiment before aortic constriction or coronary ligation was performed. This was thought to have been produced by the anesthesia and surgical manipulation. In these animals the responses to aortic constriction were identical in magnitude and timing with those of normotensive animals.

The average diastolic pressure in the left ventricle of the control period was 0 mm. Hg, and there was but a minimal elevation of it during aortic constriction in the majority of animals. In some dogs the diastolic pressure was unaffected by aortic occlusion.

In the group of experiments dealing with myocardial infarction due to ligation of a single branch of the coronary artery the results were, on the whole, analogous with those of the control group. The basal level of systolic pressure in the left ventricle after coronary ligation was about 10 mm. Hg lower, but this difference is statistically probably not significant. The response of such dogs to aortic constriction and to the release of the constriction is seen to be identical with that obtained during the control period. The one significant difference between the control period and the postinfarction period lies in the response of the diastolic pressure of the left ventricle to the increase load of aortic constriction: The basal level was considerably higher in infarcted animals and there was invariably a rise in diastolic pressure during aortic constriction (Fig. 3). The restoration of the preconstriction level, however, indicates a reversibility of this response.

The ligation of the second major branch of the coronary artery led to an invariable fall in systolic pressure in the left ventricle which in three animals was rapidly fatal, before any manipulation was possible. Two dogs were lost from ventricular fibrillation which developed shortly after the second ligation. Three animals survived the procedure and on those nine experiments were performed (Tables I and II, Figs. 1 and 2). In two of these animals severe cardiac failure associated with hypotension developed immediately after the second ligation: cardiac dilatation became visible and the diastolic pressure in the left ventricle rose. Constriction of the aorta in those two animals produced either no change, a minimal rise, or a slight fall in the systolic pressure. The diastolic pressure, on the other hand, invariably rose upon aortic constriction and did not regain the preconstriction level upon the release of the constriction (Fig. 5). The two animals lived ten and fifteen minutes, respectively, after the second infarction was produced, then died of cardiac failure. The third animal showed an entirely different response altogether. A fall in systolic pressure and an elevation in diastolic pressure in the left ventricle was also noted, but to a lesser extent than the other two animals. The response to aortic constriction consisted of a moderate elevation in systolic pressure and a rise in diastolic pressure, both of which were completely reversible. This animal persisted in a mild shocklike state without developing the rapidly progressive cardiac failure which was observed in the two other animals and had to be killed. The response to increased load in this third dog was thus intermediate between that of the other two dogs with massive myocardial infarction and rapidly progressive cardiac failure and that of animals with smaller myocardial infarcts due to ligation of a single branch.

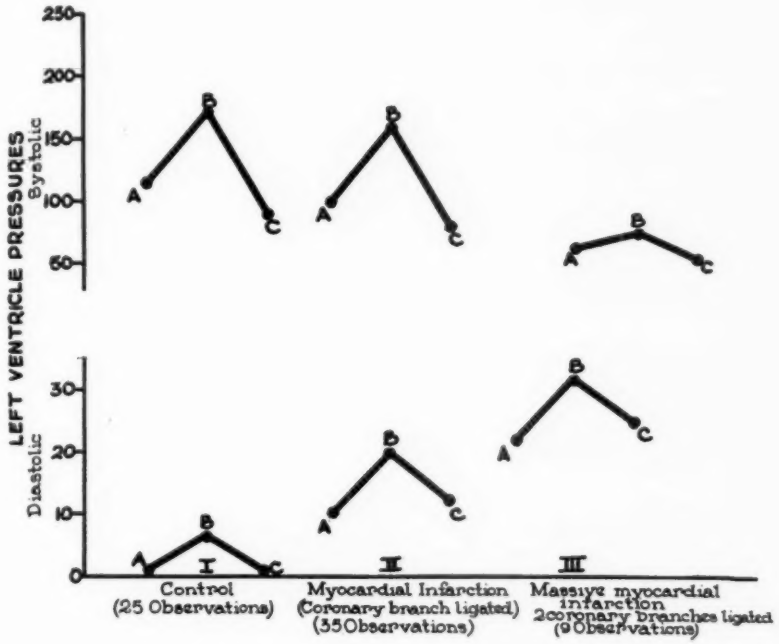

Fig. 1.—Graphic presentation of average values of systolic and diastolic pressures in the left ventricle (in mm. Hg) before (*A*), during (*B*) and after (*C*) aortic constriction, in control experiments in dogs with ligation of one branch of the coronary artery, and in those with ligation of two branches of the coronary artery (Table I).

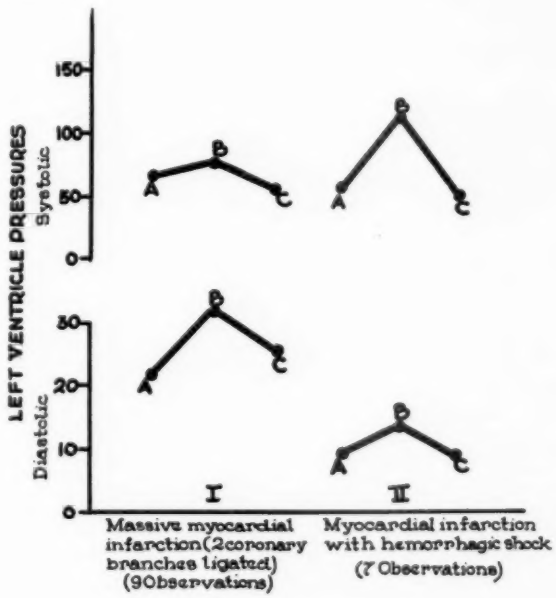

Fig. 2.—Graphic presentation of average values of systolic and diastolic pressures in the left ventricle before (*A*), during (*B*), and after (*C*) aortic constriction in dogs with hypotension due to massive myocardial infarction compared with those with smaller myocardial infarcts rendered hypotensives by bleeding (Table II).

It was pointed out that some dogs showed hypotensive levels of systolic pressure in the left ventricle before or after ligation of one branch of the coronary artery which apparently bore no relationship to the damage to the myocardium but were presumed to be due to the anesthesia and surgical manipulation. The response of these animals to the increased load of aortic constriction was identical with that of animals which had normal blood pressure levels.

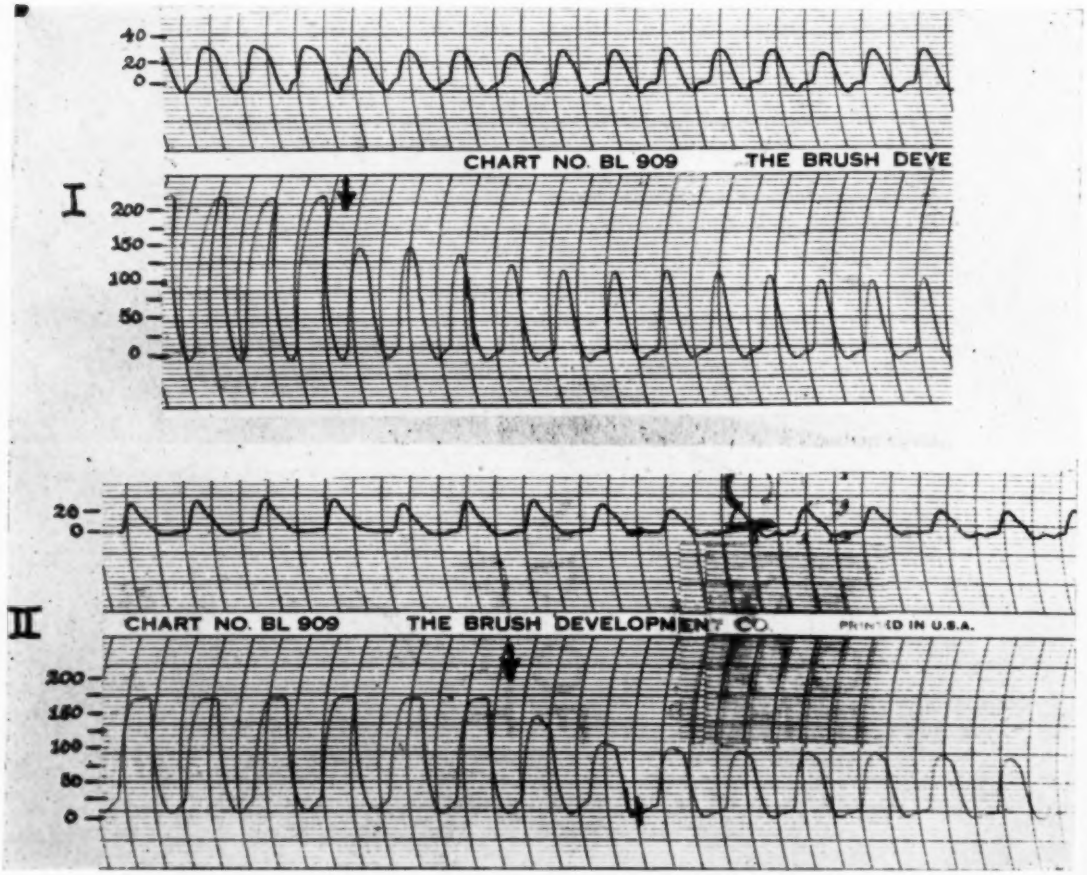

Fig. 3.—Reproduction of pressure chart of the right ventricle (upper chart) and left ventricle (lower chart) at high speed showing the release of aortic constriction (arrows) in a control experiment (*I*) and following ligation of one branch of the coronary artery (*II*). Note that the diastolic pressure in the left ventricle is not elevated in *I* and remains unchanged with release of constriction, while in *II* it is higher than normal and falls to normal levels upon release of the constriction.

In order to compare the cardiac performance of the same animals during hypotensive and normotensive states, extensive hemorrhages were induced in two animals until shock levels of systolic pressure were obtained, which was later reversed by reinfusion of the blood. Bleedings were performed in these animals both before and after ligation of a coronary artery branch. Overloading experiments were performed during state of hemorrhagic shock three times in the preligation period and seven times in the postligation period (Fig. 4). It is seen from Table II and Fig. 2 that the pressor response to aortic obstruction yielded results in shocked animals analogous to those with normal blood pressure both before and

after the production of myocardial infarction. It was noted, however, that the diastolic pressure levels and their elevation during the constriction period were definitely at a lower average level in infarcted animals in hemorrhagic shock than in those without shock.

In seven of the eleven dogs used in our study continuous tracing of pressures in the right ventricle were successfully recorded throughout the entire experiment. The effect of the overloading of the left heart upon right ventricular pressure was found to be slight and variable. An inconstant mild elevation of the systolic pressure in the right ventricle was observed in some instances, especially in those cases in which there was marked rise in diastolic pressure in the left ventricle.

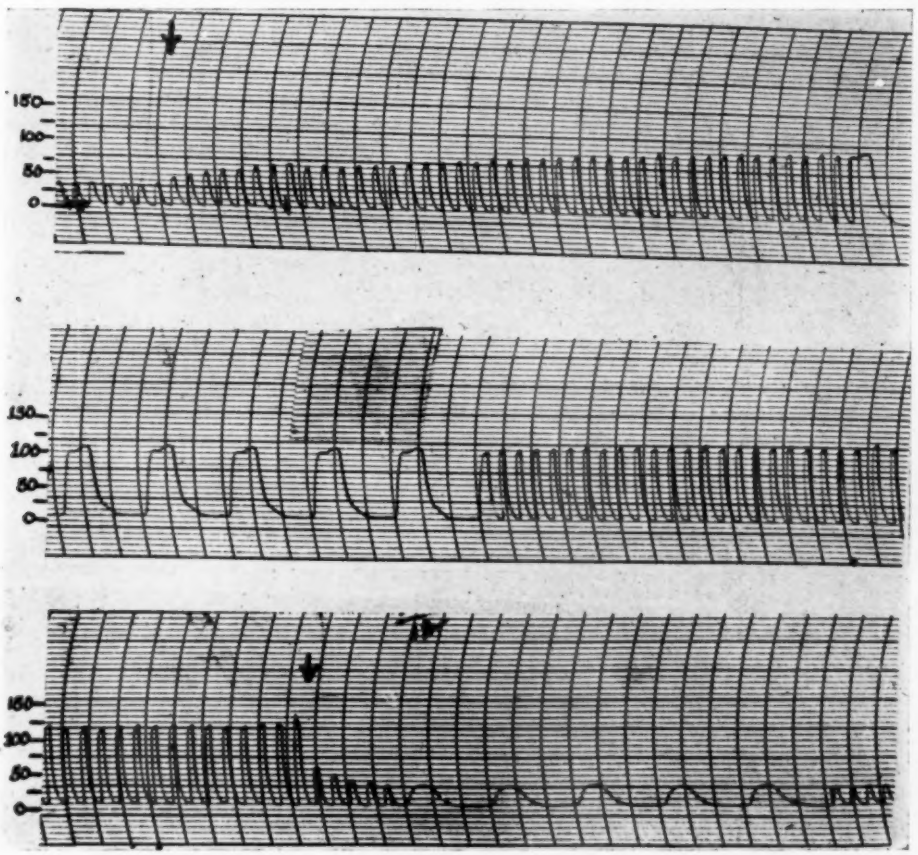

Fig. 4.—Continuous tracing of left ventricular pressure of a dog, with one branch of the coronary artery ligated, which was made hypotensive by bleeding, showing the entire period of constriction of the thoracic aorta.

In no case did the diastolic pressure in the right ventricle show an elevation. In the majority of cases, however, there was no noticeable change in right ventricular pressure tracing during our experiments. The variability of normal pressure levels and the inconsistency of the changes due to overloading experiments before and after coronary ligation lead to the conclusion that the changes in the right ventricle were not significant and they were therefore not included in the tables and charts.

DISCUSSION

Our observations were limited to the early period immediately following the formation of experimental myocardial infarction during which time the performance of the infarcted left ventricle was tested by severe pressure overload. It is shown that the ligation of a major branch of the coronary artery in the dog resulting in a myocardial infarction comparable to human myocardial infarction of average size does not materially alter the resting dynamics of the left ventricle, nor its response to overloading. The slight elevation of the end-diastolic pressure in the left ventricle in the infarcted animals as compared with controls and the

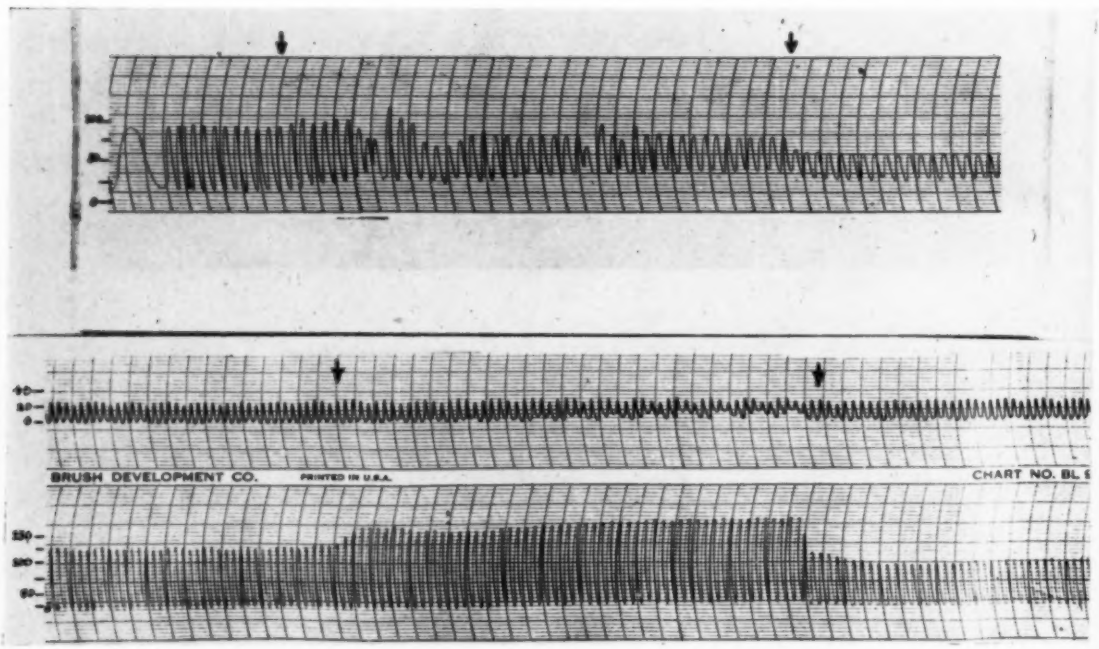

Fig. 5.—Upper tracing: Pressure curve of the left ventricle during aortic constriction and release of it (arrows) in a dog with two branches of the coronary artery ligated. Note that constriction of the aorta leads to a fall in systolic pressure and striking elevation in diastolic pressure, while upon the release of constriction the systolic pressure shows further fall and the diastolic pressure fails to reach its original level.

Lower tracing: Right and left ventricular pressures taken from a dog with one branch of the coronary artery ligated and showing the response to constriction of the aorta and its release. Note the reversibility of the elevation of left ventricular diastolic pressure, and the fall of the systolic pressure in the left ventricle below preconstriction levels.

higher increment of diastolic pressure rise in response to overloading are indicative of a circulatory derangement resulting from the infarction. However, the facts that the infarcted left ventricle is able to build up as high a pressure as the normal one, in response to increased resistance, and that the diastolic rise due to overloading is completely reversible provide ample evidence that the infarcted muscle is fully competent and the cardiac "reserve" practically normal. This conclusion is strengthened by the fact that an unnaturally strong stimulus was used to overload the left ventricle.

Observations on animals which were made hypotensive by extensive bleeding showed that the response to increased resistance was essentially the same as that of normotensive dogs. The lesser degree of elevation of the end-diastolic pressure in bled animals suggested even that the reduction of blood volume had a slightly beneficial effect upon cardiac performance. Similar observations were also made on dogs who had spontaneous hypotension unrelated to coronary ligation, which was assumed to be due to surgical manipulation and anesthesia.

Dogs that survived the ligation of two major branches of the coronary artery resulting in a massive infarction of the left ventricular myocardium showed a different circulatory response than in the case of smaller infarcts. In those animals: (1) the systolic pressure was reduced, frequently to shock levels; (2) the diastolic pressure was significantly elevated at rest; (3) in response to sudden increase in peripheral resistance the left ventricle was not able to maintain adequate systolic pressure, and (4) overloading led to further rise in end-diastolic pressure which was partially irreversible. Thus hypotension associated with such massive myocardial infarcts could be considered an example of true "cardiogenic" shocklike state in which the dilated left ventricle is unable to maintain an adequate output. It does not respond to the stretching stimulus in a manner postulated by the law of the heart of Starling[4] so that its response is placed on the descending limb of the familiar curve, as an instance of an "overstretched heart."

The distribution and variability of the results of our experiment can be interpreted as showing the spectrum of the responses of the left ventricle to the production of myocardial infarction. In smaller sized infarcts the circulation is adequately maintained by the uninfarcted myocardium and the responses to the increased load are entirely normal. In larger infarcts the resting circulation may be normal and the responses to increased load within physiologic limits, but the work is performed at the expense of increased stretching, as evidenced by the elevated end-diastolic pressure. In still larger, "massive" myocardial infarction the fall in systolic pressure and elevation of diastolic pressure, and the inadequate or abolished response to increased load, point to the loss of cardiac reserve (in the physiologic sense). Thus one can find the left ventricular performance on various segments of the Starling curve: on the ascending limb, at the top, and on the descending limb.

There is little doubt that in human myocardial infarction there is a similar pattern of circulatory derangements. In the majority of cases of coronary occlusion there is little evidence of cardiac insufficiency. In some cases left ventricular failure may be latent[5] or manifest itself as severe dyspnea and pulmonary edema. The most severe circulatory derangement takes the form of progressive cardiac failure associated with the hypotensive "shocklike" state, which is invariably fatal.[6]

No light can be shed from our experiments on the pathogenesis of the hypotensive state accompanying human myocardial infarction. It is shown, however, that "cardiogenic shock" can be reproduced in the experimental animal as a result of massive myocardial infarction which adds great weight to the interpretation of clinical observations presented in the preceding report.[6]

Finally, it should be pointed out that great caution has been applied to the interpretation of the results of our experiments, especially in comparing them with human myocardial infarction. It is fully realized that the observations were limited to the early effect of myocardial infarction upon the circulation, before any secondary changes had time to take place. Furthermore, the production of myocardial infarction in an anesthetized animal with an open chest and open pericardium may have conceivably altered some circulatory responses. However, by comparing the results of the coronary ligation experiments with control experiments performed under identical circumstances the validity of our interpretation appears complete.

SUMMARY AND CONCLUSIONS

1. Observations were made on the performance of the heart within the first two hours following the experimental production of myocardial infarction by ligating a major branch of the coronary artery in anesthetized dogs. A method is described by which the competence of the heart can be estimated by the response of the intraventricular pressure to a standardized stimulus overloading the left ventricle by increasing the peripheral resistance.

2. The performance of the left ventricle following the ligation of a branch of the coronary artery was found to be normal, comparable to control experiments, although slight elevation of the end-diastolic pressure was frequently observed.

3. In dogs rendered hypotensive by extensive bleeding the performance of the left ventricle following myocardial infarction was the same or even better than in normotensive dogs with myocardial infarction.

4. True "cardiogenic shock" or hypotensive state was reproduced in dogs by ligating two major branches of the coronary artery, thereby producing a massive myocardial infarction. This state was characterized by (a) hypotension, (b) marked elevation of the end-diastolic pressure in the left ventricle, (c) inability of the left ventricle to elevate the systolic pressure in response to an increase in peripheral resistance, and (d) partially irreversible further elevation of the diastolic pressure brought on by the overloading stimulus.

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THE NORMAL CARDIAC APEX AND APEX BEAT: A CRITICAL REVIEW OF RECENT DATA

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THE STUDY of the normal range of variation is a matter of considerable practical importance—"Pour connaître homme malade, il faut connaître homme sain." It is of interest, then, to compare certain former cardiac data with figures more recently published by Isaac and Levy.[1] These authors defined the apex beat as the farthest inferolateral point of maximal pulsation, but they reminded us that other definitions are used. Thus, Bramwell and King[2] preferred the central point of pulsation because ". . . the term 'maximal impulse' refers to a small area only, and it is much easier to locate with certainty the centre of that area than its periphery." Bourne[3] stated that the apex beat should be found over an intercostal space, as it may be localized incorrectly over a rib. With regard to mensuration in a horizontal direction, Isaac and Levy found 8.9 cm. (3.5 in.) from the midsternal line as the maximal incidence of the apex beat in 134 out of 395 recumbent male subjects. The variation was from 5 to 14 cm. (2 to 5.5 in.), and the apex beat was more than 10 cm. (4 in.) from the median line in forty-five cases. Apart from these forty-five cases the figures agreed fairly closely with those of Mainland and Gordon[4] who, using a similar definition of the apex beat, found that ". . . the mean distance of [the normal male] apex beat from the midsternal lines was 7.62 cm. [3 in.] in 75 erect subjects, 8.31 cm. [3.25 in.] in fifty-three recumbent subjects." The estimated normal range ($2x$ standard deviation) was 6.0 to 9.2 cm. (2.25 to 3.5 in.) (erect), 6.4 to 10.2 cm. (2.5 to 4 in.) (recumbent). The midclavicular line has been discarded as a landmark by most workers.

A number of writers (for example, Skinner[5]) have stressed the importance of the size of the thorax, and Bramwell and King[2] considered that ". . . the statement that the left border of the heart is so many centimetres from mid-sternum is valueless, unless one also knows the size of the chest." Mainland and Gordon[4] maintained that although a wider thorax tends to contain a wider heart, nevertheless, for a given width of thorax, they found no adequate evidence that ". . . tall and short thoraces differed from each other in respect of the distance of apex beat from midsternal line." The thoracic width is allowed for by Eve[6] who measured the "heart angle" in angular degrees (Fig. 1). "The midsternal line is taken as 0° and the midaxillary line as 90°. The position of the apex beat

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[leftmost palpable 'border,' sitting, or standing if possible] is then expressed as a figure between these two." We may represent it thus mathematically:

$$a = \frac{b}{c} \times 360$$

where *a* is heart angle in degrees, *b* is distance of beat from midsternum, and *c* is circumference of thorax. In practice a chart is used to read off the angle. The advantages claimed for this measurement are that it is not affected by growth, it relates "apparent" heart size (that is, in terms of apex beat) to chest size, and allows a normal to be laid down. In 250 first-class insurance lives the range was from 27 to 44 degrees, and all except thirty were between 30 and 40 degrees. Eve also examined the results in 200 naval ratings, 70 laborers, and 140 school children; those indulging in physical work tended to have an increased angle, but the normal laid down was that ". . . both in children and adults it lies between 30° and 45°." Isaac and Levy, on the contrary, found less than 2 per cent difference in the average girth of the total series and those with apex beat more than 4 in. from the midsternum. They concluded that ". . . there would seem to be little to bear out the assumption of a direct relationship between the girth of the chest and the position of the apex beat." In the total series (500 cases) the average girth was 34.6 in. and in the palpable cases the average distance of the apex beat was 3.5 in. The average girth for the palpable cases is not given but we may take the average heart angle as being:

$$a = \frac{b}{c} \times 360 = \frac{3.5}{34.6} \times 360 = 36.4 \text{ degrees}$$

In the forty-five cases with apex beat more than 4 in., the average girth was 35.1 in. The average distance of the apex beat is not recorded but it must have been between 4 and 5.5 in. We cannot calculate the extreme values for the heart angle in this group from such data but by using the average girth we would get:

$$a = \frac{4}{35.1} \times 360 = 41.0 \text{ degrees, and } a = \frac{5.5}{35.1} \times 360 = 56.4 \text{ degrees}$$

It will be noticed that the last figure, or even the mean between the two figures (48.7 degrees), is outside the limit set by Eve's standard.

Isaac and Levy found that approximately one-quarter (22.6 per cent) of their total series and about the same fraction (26.6 per cent) of the forty-five cases already alluded to showed scoliosis. A marked preponderance of scoliosis to the left was apparent in those cases over 4 in. from midsternum (five left; one right) as compared with the total series (two left; one right). Some of the forty-five cases, however, had no scoliosis, and in such instances ". . . another cause must be sought . . .," for example, height of diaphragm, sternal depression. With reference to the normality or otherwise of cases showing an apex beat a large distance from the sternum, the following remarks of McKinlay and Walker[7] on blood pressure in healthy adults are particularly apposite: "The variability of physiological measurements such as these is not sufficiently recognized either in standard textbooks or in actual clinical teaching. As regards blood pressure, the frequency

with which one hears not only experienced medical men, but even the veriest tyro in medicine state that a given blood pressure is above or below 'normal' is sufficient in itself to indicate the ignorance which exists as to the range of values compatible with health." They conclude: "The differences in blood pressure which we have found in these healthy men are such that we would have great hesitancy in believing any isolated measurement in otherwise apparently fit individuals to be abnormal. They indicate the need for further extensive study of the interrelationships of all the bodily measurements in man with a view to determining the prognostic significance of such deviations."

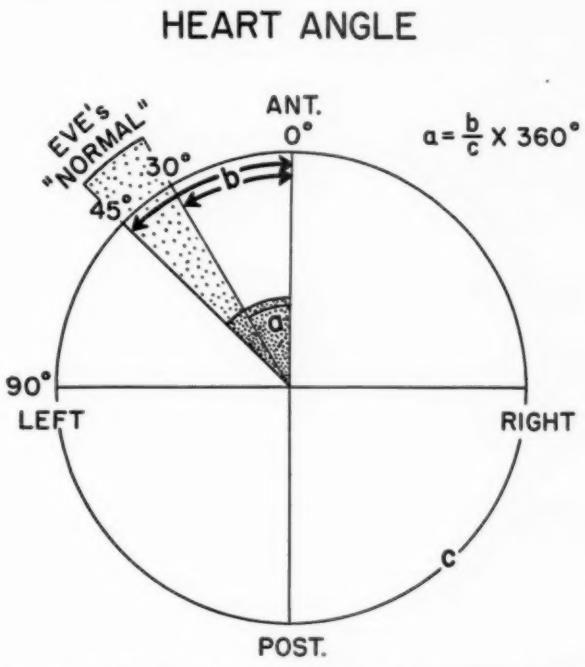

Fig. 1.—The "heart angle" (after Eve[6]). *a*, "Heart angle" in degrees; *b*, distance of the apex beat from the midsternum; *c*, circumference of the thorax.

$$a = \frac{b}{c} \times 360 \text{ degrees}$$

The shaded area indicates the "normal" range according to Eve.

Second, as regards vertical localization, Isaac and Levy[1] found the apex beat ". . . almost equally in the 4th and 5th intercostal spaces, and only in a very few in the 3rd and 6th intercostal spaces." For comparison, it may be mentioned that Mainland and Gordon[4] found that the apex beat was in the fifth intercostal space in eighty out of eighty-two erect subjects and in fifty out of fifty-four recumbent subjects, and thus rarely in the fourth (one erect and four recumbent cases) or sixth (one erect case) intercostal space; they do not record having found it in the third space.

In the above discussion only those cases in which the apex beat could be localized have been mentioned; these proved to be the great majority (395 out of 500, recumbent, Isaac and Levy; sixty out of eighty-six, recumbent, and eighty-two

out of eighty-six, erect, Mainland and Gordon). Similarly, Eve[6] records that in only one out of fifty men examined was the apex beat impalpable. Niehaus and Wright,[8] however, in the examination of 1,000 normal persons found the apex beat (which they defined as the point of maximal intensity of the impulse) as a definite visible and/or palpable location (erect, prone, or only leaning forward) in only 24 per cent. It was easier to determine at younger ages, in women, and in those of lighter weight. Isaac and Levy examined ages 17 to 42 (62.2 per cent were between 17 and 20, 33.0 per cent between 21 and 30, and only 4.8 per cent between 31 and 42); Mainland and Gordon from 19 to 25 (and three other cases, the maximum being 32 years). Niehaus and Wright covered a wider age range but they found that ". . . up to 20 years of age, the apex [beat] can be distinctly felt in 54 per cent of males and 55 per cent of females; between 20 and 30 years of age it drops to 27 per cent of males and 39 per cent of females." It must be remembered that special methods are used by some workers to elicit an apex beat otherwise not palpable; thus, Dressler[9] recommended applying considerable pressure against the ribs in difficult cases.

APEX CORDIS

Third, concerning the relation of the apex beat to cardiac topography, Isaac and Levy did not employ routine radiography in their investigations, but in occasional skiagrams of cases presenting an apex beat more than 4 in. from midsternum, they record that ". . . the apex beat as found clinically corresponded with the apex of the heart radiologically." This apex, however, is not defined, nor is mention made as to the type of radiography employed.

"Apex," in the words of Dorland[10], is a Latin term meaning ". . . the top or pointed extremity of any conical part." The apex of the heart, the same author continues, is ". . . the blunt rounded extremity of the heart represented by the left ventricle." The cardiac apex is sometimes referred to as the inferior pole or the inferior left corner of the heart. Radiologically, the summit of the ventricular cone may appear so blunt and rounded as to render the term "apex" as highly misleading as the term "McBurney's point" is in the appendicular region (O'Rahilly[11]). This obtuseness is illustrated by Laubry and associates[12] in their schematic composition of the normal median thoracic shadow (Fig. 63, p. 31, of their book) and these authors prefer to speak of ". . . the region of the apex." Furthermore, the radiologic apex may be formed by a different anatomic part in differently orientated hearts. Laubry and associates point out that if the heart is small and vertical with its long axis towards the front, the anatomic apex is placed a little medial to the tangential ray; on the contrary, when the heart is "lying down," its long axis tends to become parallel to the screen and the anatomic apex is tangential to the radiation. In the first case, the region of the apex is a blunt curve; in the second, the apex takes up an angular form.

Apart from the lack of a radiologic apex, in a number of hearts the anatomic apex is likewise conspicuous by its absence. Keith[13] found in nine out of fifty-five normal cases (16 per cent) at autopsy a "globular type" of heart ". . . the absence of any apex being most striking." These hearts were in a younger age group (average age 48) than those of the other types described. The same writer found

that the normal anatomic apex is formed by either the left ventricle or the ventricular septum, but not by the right ventricle (however, cases where the apex was formed by the right ventricle have been described—Merkel, cited by Mall,[14]); ". . . the composition of the apex was determined by the position of the anterior descending branch of the left coronary artery whose course marks out the position of the interventricular septum." We take this to mean that in Keith's cases the apex either was crossed by, or was on the lateral side of, the interventricular branch (ramus descendens anterior, BNA) of the left coronary artery; Vaquez and Bordet[15] found that the summit of the apical region corresponded with the interventricular groove in the elongated heart but that the most prominent point of the ellipsoidal curve in the globular heart was above (and lateral to — their Fig. 9) the interventricular sulcus.

The diaphragm, in spite of its mobility, has been used as a radiologic landmark for the cardiac apex, although little agreement has been reached as to the interrelationship between the two structures. Luisada and associates[16] plot ". . . the apex of the heart just above the diaphragm" in fluorocardiography (electrokymography). Mainland and Gordon[4], in teleradiograms of 110 normal students found that ". . . in the films used for the estimation of its position [the apex] there was an indication that the lower part of the left cardiac border was commencing to turn medially as it met the stomach shadow." However, Tillier[17] has warned us that ". . . the intersection of the diaphragm and the left contour of the heart does not constitute a fixed point utilizable for measurements . . .," and in some adipose individuals the diaphragm may be so high that its shadow bisects the transverse cardiac diameter (Bourne and Wells[18]). Kurtz and White[19] found that ". . . sometimes the apex of the heart shadow in the 7-foot plate is so buried in the shadow of diaphragm and abdomen that the identification is largely guess work and less accurate than the position of the apex impulse as determined by palpation on physical examination . . ." and Köhler[20] spoke in a similar vein of the ". . . greater or less degree of imagination . . ." required in filling in superior and inferior cardiac margins. Groedel[21] stated that according to Otten the radiographic apex was projected:

POSITION	BELOW LEVEL OF DIAPHRAGM	ABOVE LEVEL OF DIAPHRAGM
Lying	85 times	12 times
Sitting	79 times	13 times
Standing	93 times	0 times

Vaquez and Bordet[15] found that a parallel to the basal diameter (joining right and left ends of the atrioventricular groove) is tangential through a point situated in the immediate vicinity of the interventricular groove; and this point, "G′," is used as the apex.

Roesler[28] emphasizes that the left lower pole region does not indicate the caudal limit of the heart, for, on rotating the subject into the left anterior oblique position, the lower left corner is 0.5 to 2 cm. more caudal in two-thirds of all cases.

A given point in the apical region will vary in its relation to the diaphragm (Vaquez and Bordet[15]) and, according to Laubry and associates,[12] the apex is not apparent during quiet respiration, being concealed by the diaphragmatic shadow. But the two structures can be separated by a deep inspiration (Vaquez and Bordet, Laubry and associates, Wolferth and Margolies[22]). "Roentgenologic examinations have shown how decisively the shape of the heart is influenced by the position of the diaphragm . . ." (Dressler[47]) and in deep inspiration the ". . . distinct contour becomes less marked . . ." (Dorland and Hubeny[23]) so that the apex, although more visible, is more difficult to define. "A gas-filled stomach bubble often enables one to visualize the apex, and is of considerable aid in determining the true extent of the left ventricular segment" (Epstein[24]).

A further complication in the apical region is the triangular shadow sometimes seen in the cardiophrenic angle. This is probably due to ". . . epipericardial fat . . ." attached to ". . . the outer side of the parietal pericardium . . ."* (McGinn and White[25]) in the pericardiacophrenic ligament — "le ligament phrénopéricardiaque" (Laubry and associates[12]). According to Walmsley[26] ". . . the left phrenico-pericardial ligament (of Teutleben) is the name given to a rather weakly developed tract of fibres which is attached to the left margin of the central tendon of the diaphragm and ascends on the left surface of the pericardium as far as the root of the left lung. It is much less easily defined than the right ligament." Köhler[20] describes the cardiophrenic shadow as ". . . neither more nor less than the stretched left lateral wall of the pericardium . . ." seen in deep inspiration.

A short distance to the right of the apex is a slight depression on the inferior border of the heart where the anterior and inferior interventricular (anterior and posterior longitudinal, BNA) grooves are continuous with each other (Walmsley[26]), the "incisura apicis cordis." Radiologically, this indentation ". . . can be identified in the right oblique position, and occasionally is demonstrable in the postero-anterior position through the stomach bubble" (Epstein[24]). A deep incisura gives the appearance of a bifid apex, and a number of such cases have been recorded (for example, Harris[27]); it is attributed to the absence of the muscular vortex at the apex (Mall[14]).

There is no doubt, then, but that the apex is ". . . admittedly a difficult region to locate . . ." (Mainland and Gordon) and it may be concluded from the above discussion that the term is of highly questionable value in many cases since ". . . it is obviously impossible to determine in any of the projections a localized 'apex' or even the general direction of this apex or lower pole . . ." (Roesler[28]).

RELATIONS BETWEEN APEX BEAT AND APEX CORDIS

However, prescinding now from the indefinite nature of the apex, Mainland and Gordon,[4] on their criteria (quoted above), found that the mean (modal) position of the lower left corner was on the sixth costal arch, 7 cm. (2.75 in.) from the midsternal line, and 5 cm. (2 in.) below the level of the xiphisternal joint,

*The term "extrapericardial" (cf "extrapleural" and "extraperitoneal") would seem preferable to the present writer.

erect posture; fifth space, 7.5 cm. (2.75 in.) from midsternum, 3 cm. (1 in.) below joint level, recumbent posture. By comparing teleradiographic and clinical data they concluded that the apex beat ". . . was on the average above and slightly lateral to the true apex, but coincided with the left heart border, erect and recumbent . . ." at the time when the beat was noted.

There is considerable divergence of opinion as to the relation which the apex beat bears to the cardiac apex and cardiac outline. Dietlen noticed in 1907, according to Fossier,[29] that ". . . the apex is almost always felt one interspace higher than the apex of the silhouette obtained by orthodiagraphy, or if the apex beat is under a rib, at least the width of one finger higher." He attributed this to palpation during systole and radiography during diastole, and so apparently assumed that the apex and the apex beat should be coextensive. That the apex beat may be lateral to the apex comes as a surprise to some writers. Foti[30] found that the impulse ". . . hardly, if ever, corresponds to the apex of the orthodiagram but is found above the latter, inside and sometimes even to the left of the outer [left] border of the cardiac contour." But in the case of a narrow thorax, he added, the movement of the impulse may be laterad toward the side of the chest rather than forward; occasionally, in the vertical heart displacements of the impulse to the right (and also downward if pronounced) may be observed. Smith[31] assumed that the impulse should be medial to the apex, although ". . . for practical purposes the maximal cardiac impulse gives a rather accurate indication of the site of the left border of the heart." Smith reproduced skiagrams with metal markers over the impulse to prove his point but omitted mentioning what type of radiography was used and whether corrections for distortion were made—furthermore, he was referring to the center of the impulse. He added that in a few normal persons with thin thorax and rather elongated heart the impulse was lateral to the left border of the heart. According to Zdansky,[32] ". . . the palpable apex beat coincides only in one-third of all cases with the radiological cardiac apex (Dietlen). In most cases it lies 1 to 2 cms. cranial and medial to it (G. Schwarz, Dietlen, Sahli). This has been explained by the fact that it is not so much the cardiac apex, overlapped by the lung, that produces the apex beat, but the systolically contracting anterior wall of the ventricle.* Only in the narrow chest can the apex beat be located lateral to the left cardiac margin (Dietlen). In the agitated heart, after physical exertion, after excitement or in thyrotoxicosis, the pulsatory excursions of the chest wall can extend considerably to the left, beyond the contour of the heart, also in the

*It should be remembered that the lower part of the anterior margin of the left pleura has not been visualized so far in the intact living body. It is described as following the sternal margin below the level of the fourth costal cartilage, not forming a marked notch as in traditional illustrations, although considerable variation occurs (Woodburne,[34] 102 cadavers) but it has also been claimed that it has a similar course to that on the right side (in 90 of 100 cadavers), forming no cardiac notch (Noback[35]) and the pleura of either side may cross the median plane (Morris,[36] after Tanja). A similar doubt as to the condition in vivo occurs in regard to the extent to which the lungs fill the costodiaphragmatic recesses behind (Lachman[37]). It is of interest to recall that the sites of the cardiac valves in vivo, unknown for so long, are now being elucidated. The older methods (Groedel,[38] Norris and Fetterolf,[39] LeWald[40] and Rouvière[41]) related to formalin-fixed cadavers. In abnormal hearts the valve positions can be determined radiographically in vivo when the valves are calcified (Sosman and Wosika[42]). Normal valves can be investigated by angiocardiography; Parkinson[43] stated that the aortic valve lies ". . . almost in the centre of the heart shadow as seen from in front, and in the middle line or to the left of it . . . . The mitral valve is close to it, a little lower and to the left."

normally configurated chest (Moritz)." Treadgold and Burton,[33] found, in 100 healthy erect men (18 to 40 years), that the leftmost point at which a definite purely forward lift was felt by the finger tip corresponded to the anatomic apex as seen in orthodiagrams in 40 per cent; in 27 per cent the apex beat corresponded to the left border above the apex; in 25 per cent the apex beat was 1 or 2 cm.

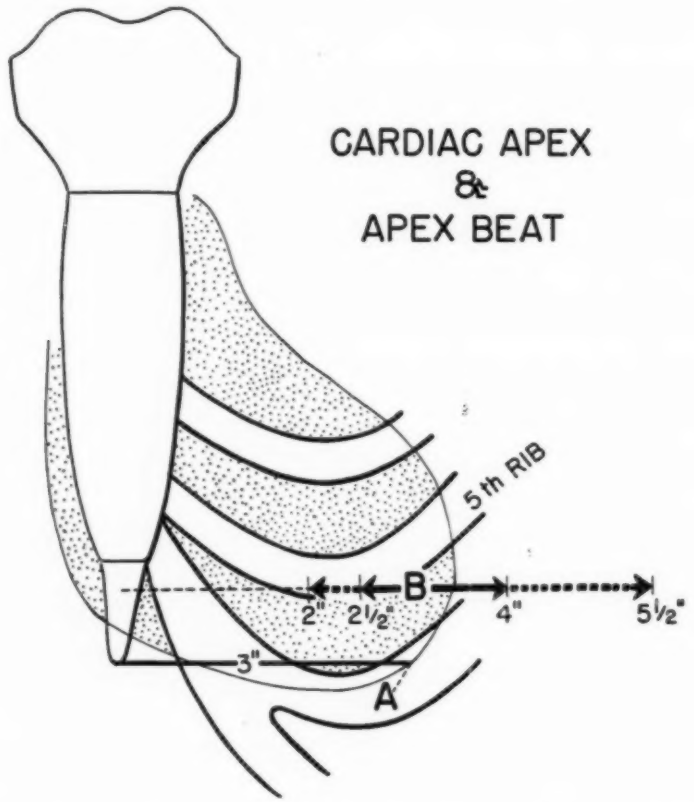

Fig. 2.—Usual positions of the cardiac apex and apex beat. The apex (*A*) is commonly in the fifth intercostal space, 3 inches from the midsternum, and below the level of the xiphisternal joint. It is slightly lower in erect than recumbent position.

The apex beat (*B*) is usually in the fifth or fourth intercostal space, and 2.5 to 4 in. (heavy solid line) from midsternum, but extremes of 2 to 5.5 in. (heavy broken line) from midsternum have been recorded in apparently normal subjects. It is slightly more medial erect than recumbent.

The apex beat (*B*) is generally above the apex (*A*) and often is lateral to it, but it may be medial.

lateral (and in 8 per cent medial) to the apex or the left border. According to Roesler[28] the apical thrust ". . . is usually found to be located 1 to 4 cm. above the roentgenologic lower pole and it is approximately thrice as frequent outside the silhouette as inside . . .," particularly in a narrow chest and during cardiac overactivity, for example, exercise. Braus and Elze[44] also maintained that the apex is medial to the apex beat, which "irradiates" laterally. Köhler[20] cited Moritz that sometimes the apical impulse appears outside the cardiac outline due to the oblique direction of action of the impulse. Walmsley,[26] however, was of

the opinion that the apex beat lies about one-half inch medial to the apex; the grounds for this view were not given.

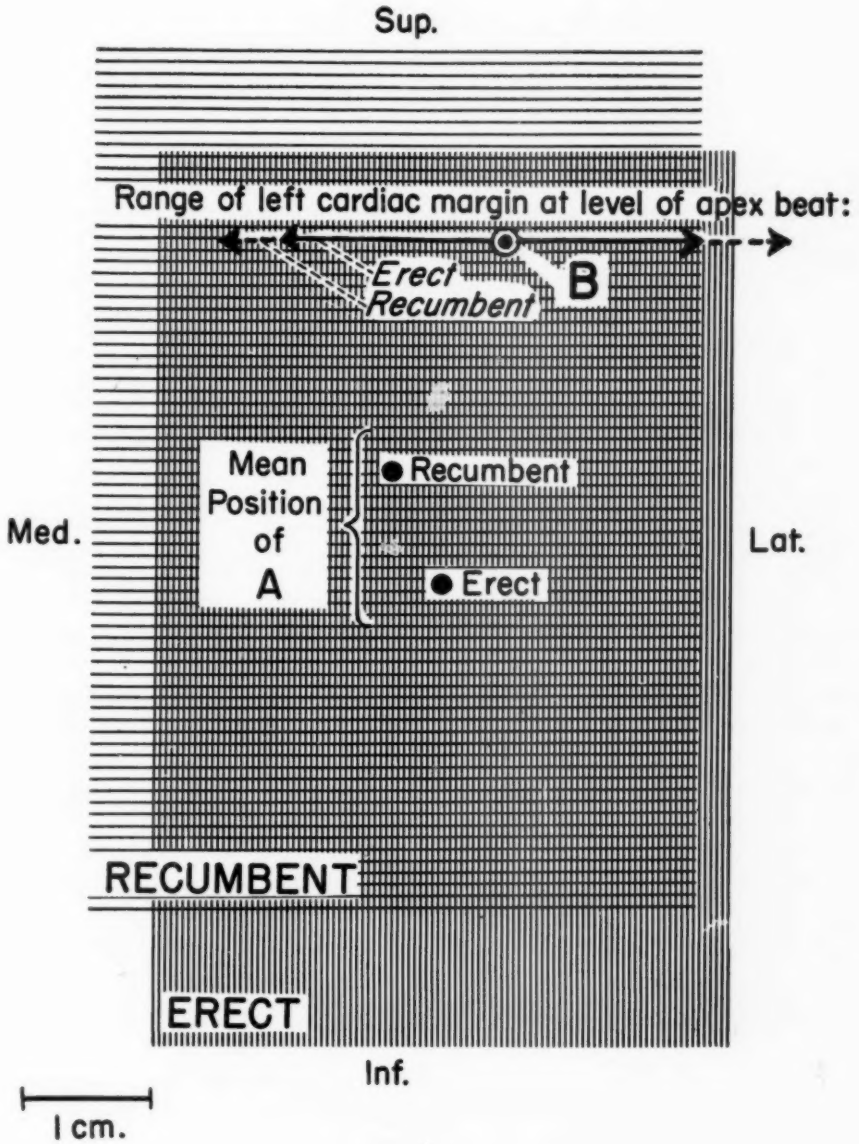

Fig. 3.—The interrelationships between the cardiac apex and apex beat. *B*, The apex beat, has been selected as a fixed point (owing to the lack of an acceptable definition of the apex). The rectangles surrounding *B* contain the possible positions of *A*, the apex, which would be expected from the estimated normal range (2 S.D.) of Mainland and Gordon's data. The vertical-line rectangle refers to the erect, the horizontal-line rectangle to the recumbent posture. The mean positions of *A*, the apex, erect and recumbent, are indicated by dots. The arrows on either side of the point *B* show the extent of the estimated normal range of the left cardiac margin (which may thus be either to the right or to the left of the apex beat).

With regard to the statements of Mainland and Gordon, it is difficult to see how a point on the left margin coincident with the apex beat could be lateral to a point where the left margin was ". . . commencing to turn medially." (See Fig. 2.) With a view to visualizing better the interrelationships between the apex and apex beat, a diagram (Fig. 3) has been prepared by the present writer from the tables provided by Mainland and Gordon. Owing to the lack of an acceptable definition of the cardiac apex, the apex beat (*B*) has been selected as a fixed point for the erect and recubment postures, and around it rectangles have been constructed containing the *possible* positions of the apex (*A*) as recorded in the estimated normal range (2 S.D.) in the original paper of the above authors. The estimated normal range of the left cardiac margin was 1.75 cm. (0.75 in.), erect, to right or left of the apex beat (2.25 cm. (1 in.), recumbent.) This is recorded in Fig 3 by the arrows on either side of *B*.

ADDITIONAL FACTORS

The chief factors which affect the form and position of the viscera (O'Rahilly[45]) are: race, sex, age, individual variations, habitus, posture, respiration, tone, contents, intrinsic movements, and condition of adjacent viscera. Some of these factors are of special import in the role they play in affecting the cardiac apex. They have been well summarized by Lachman,[46] and it is not necessary to reiterate them here. Neither is it proposed to discuss here the exceedingly complicated and disputed cardiac movements.

Most writers consider that the cardiac impulse ". . . is not a simple projection of the apex on the chest wall but results from the motions of the left ventricle during systolic contraction" (Foti[30]). According to another view, however, the impulse ". . . is produced by the impact of a portion of the right ventricle against the wall of the thorax . . .," although ". . . in cases in which the heart is weak, hypertrophied and dilated, the striking of both the right or left ventricles against the thoracic wall can be demonstrated (Smith[31]). It would seem improbable that the right ventricle would produce an apex beat to the left of the cardiac outline but the apex beat is generally taken as the most inferolateral part of the impulse, whereas the last-quoted author is referring to the center of the impulse.

SUMMARY

1. There is a lack of agreement concerning the clinical localization of the apex beat. A commonly used definition employs the farthest inferolateral point of maximal pulsation. Only a certain proportion of apex beats can be localized by palpation; this varies from 24 to 98 per cent in the recorded literature.

2. As regards horizontal localization, the mean distance of the adult apex beat (as defined above) from the midsternum is 3.25 or 3.5 in. in the recumbent posture, 3 in. when erect. The variation is commonly from 2.5 to 4 in. from midsternum, recumbent, and 2.25 to 3.5 in., erect, but extremes ranging from 2 to 5.5 in. have been found in apparently normal subjects. Here, as elsewhere, the wide range of physiologic values compatible with health should be stressed.

The existence of a direct relationship between the width of the thorax and the position of the apex beat is disputed; its possibility is allowed for by "heart angle" measurements.

3. As regards verticle localization, the apex beat is commonly in the fifth, or perhaps in either the fourth or fifth, intercostal space, rarely in the third or sixth.

4. The apex cordis is formed by either the left ventricle or the ventricular septum, rarely by the right ventricle. Radiologically, the apex is influenced by the orientation of the heart and body, and the cardiac contour is frequently such that no apex is definable. This is in agreement with the observation that 16 per cent of normal hearts have been found to show no anatomic apex post mortem. The radiologic apex has been defined either in terms of cardiac geometry or variously as being above, at, or below the diaphragmatic shadow; the relationship between the heart and diaphragm is too inconstant to be satisfactory, however. An acceptable definition of the radiologic apex cordis does not seem to be available and it is questionable whether the term "apex" has any value as a localized landmark in many cases.

5. The mean position of the apex, definied (however questionably) as the inferior left corner of the heart, is recorded as being in the fifth intercostal space, 2.75 in. from midsternum, 1 in. below the level of the xiphisternal joint, recumbent; sixth costal arch, 2.75 in. from midsternum, 2 in. below the joint level, erect. It appears that the apex beat is usually above the apex, and that it may be lateral (commonly) or medial to the apex or to the left cardiac margin.

6. The apical region of the heart is affected by a number of factors, such as posture, respiration, and habitus. The intrinsic cardiac movements are exceedingly complicated and much further work remains to be done toward their elucidation. The mechanism of the apical impulse appears to be in doubt.

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AXIS DEVIATION AND BODY BUILD

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IN 1913 Einthoven, Fahr, and DeWaart[1] published a method of estimating the direction and manifest magnitude, at a given instant in the cardiac cycle, of that component of the heart's electromotive force which is parallel to the plane defined by the standard limb leads. The literature is filled with experiments which were designed to demonstrate[2,3] and question[4,5] the validity of Einthoven's hypothesis.

There also have been a number of clinical and anatomic studies in which various body measurements have been correlated with size of normal hearts[6,7] as well as anatomic consideration of the heart in its relationship within the thoracic cage. In view of the interest in these correlations between somatic measurements and size of the heart, it is surprising how little data are available on correlations of these somatic measurements with the electrical axis. Bland and White[8] and Master and Oppenheimer,[9] in studying the clinical significance of complete inversion of Lead III, concluded that obesity with a high diaphragm was the cause in the majority of instances in normal individuals. No somatic measurements or morphologic variations were included in these papers. Comeau and White,[7] in studying body build and heart size, expressed the opinion that at that time the ponderal index (that is, an expression of height and weight) was the best known index of body build but was not entirely satisfactory in expressing body mass. This difficulty has been surmounted by Sheldon and associates[10] who have presented, by the system of somatotyping, a method based on anthropometry which is a more reliable index for expressing body build and, hence, body mass. By employing this systen it is possible to correlate heart size and electrical axis with body build as expressed in the most definitive manner known at this time.

It is the purpose of this paper, therefore, to (1) present correlations between electrical axes of 144 normal men and several of their anthropometric (somatic) measurements and indices; (2) to present a more reliable index as to the influence of body morphology on electrical axis as expressed by the Einthoven technique, and (3) to consider the possible clinical significance of these studies.

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METHOD

As a part of a larger and more inclusive study of coronary heart disease, routine electrocardiograms, including standard limb leads checked by unipolar limb leads, were taken on 144 normal men who did not show any clinical or laboratory evidence of heart disease. The electrocardiograms were taken in accordance with the method recommended by the American Heart Association. These individuals were also employed as a control group in an extensive study of coronary heart disease by one of us. The axis deviation in degrees in each individual was determined from the standard limb leads by direct measurement on an Einthoven triangle. Each subject was photographed and somatotyped by the method proposed and described by Sheldon and associates.[10] In addition, certain other body measurements were taken.* These are listed in Tables I and II.

TABLE I. COEFFICIENTS OF CORRELATION BETWEEN AXIS DEVIATION (ECG) AND ANTHROPOMETRIC MEASUREMENTS AND INDICES

Height	$+0.05 \pm 0.08$
Sternal ensiform	-0.03 ± 0.08
Chest depth	-0.20 ± 0.08*
Chest ratio D/W	-0.21 ± 0.08*
Chest width	-0.25 ± 0.07†
Weight	-0.33 ± 0.07†
Ponderal index	$+0.36 \pm 0.08$†

*Significant ($p > 0.05$).
†Highly significant ($p > 0.01$).

Sheldon's method of somatotyping physique is classified into a continuum of three components, namely, endomorphy (softness and roundness), mesomorphy (angularity and muscularity), and ectomorphy (linearity). Each of these three components is given a numerical rating[1-7]; accordingly, the numerical value of these ratings may be employed in calculating correlation coefficients. Thus a 3-7-1 somatotype would be an individual who possesses three degrees of endomorphy, seven degrees (maximal) of mesomorphy, and one degree (minimal) of ectomorphy.

TABLE II. COEFFICIENTS OF CORRELATION BETWEEN AXIS DEVIATION (ECG) AND SOMATOTYPE DOMINANCES

Endomorphy	-0.37 ± 0.07*
Mesomorphy	-0.15 ± 0.08
Ectomorphy	$+0.34 \pm 0.07$*

*Highly significant ($p > 0.01$).

RESULTS

The coefficients of correlation on the 144 individuals between axis deviation and various anthropometric measurements are presented in Tables I and II.

*These were accomplished by Dr. Stanley M. Garn of Harvard University.

TABLE III.

NO.	AXIS DEVIATION	SOMATOTYPE	WT.	HT.	PONDERAL INDEX $\left(\frac{\text{HT.}}{\sqrt[3]{\text{WT.}}}\right)$
1	−40	5 −2 −3	181	172	11.9
2	−30	4 −4 −2²	175	173	12.1
3	−30	2 −4 −5	171	177	12.6
4	−30	2 −3 −5²	172	182	12.9
5	−28	4 −5²−1	194	178	12.1
6	−22	3 −4²−3	195	184	12.5
7	−15	5²−4 −2	195	177	12.0
8	−15	5 −4²−2	190	184	12.6
9	−10	4 −4²−2	177	174	12.2
10	− 3	6 −6²−1	235	178	10.9
11	− 3	4 −3 −4	170	177	12.5
12	0	6 −4²−1	205	175	11.7
13	0	6 −3 −2²	179	174	12.1
14	+ 5	6 −3²−1	163	162	11.6
15	+ 7	4²−5 −1	216	179	11.7
16	+ 8	3 −6 −1	188	170	11.7
17	+10	5 −4 −2²	190	182	12.4
18	+10	4 −5²−1	194	175	11.9
19	+12	5 −4 −2	190	184	12.6
20	+12	4 −5 −2	185	172	11.9
21	+12	4 −4 −3	155	171	12.6
22	+13	4 −5 −3	208	192	12.7
23	+15	5 −6 −1	196	171	11.6
24	+19	6 −4 −1	231	190	12.2
25	+19	5 −4 −2	215	187	12.2
26	+20	6 −4 −1	189	178	12.1
27	+20	5 −5 −1	250	192	11.9
28	+20	4 −5 −2	161	165	11.9
29	+21	6 −5 −1	238	178	11.2
30	+21	5 −4 −1	171	172	12.2
31	+24	5 −3 −2	185	178	12.2
32	+25	5 −4 −2	178	183	12.8
33	+25	4²−5 −2	178	169	11.8
34	+26	5 −2 −3	175	177	12.4
35	+28	6²−3 −2	204	178	11.9
36	+29	6 −4 −1	176	170	12.0
37	+29	6 −3 −1	179	167	11.7
38	+30	6 −4²−1	230	186	11.9
39	+30	5 −5 −1	200	168	11.3
40	+39	5 −4 −2	170	174	12.3
41	+30	5 −4 −1	185	176	12.2
42	+30	5 −6 −1	206	179	11.9
43	+30	5 −5 −2	187	175	12.1
44	+30	3²−6 −1	191	175	12.0
45	+30	3 −4²−3	164	179	12.9
46	+30	3 −4 −3	181	182	12.6
47	+30	2²−3²−2²	168	172	12.4
48	+30	2 −3 −5	134	165	12.7
49	+30	3 −5²−2	154	169	12.3
50	+33	2 −3 −6	165	186	13.3
51	+35	5 −4²−2	186	181	12.5
52	+35	4 −5 −1	180	169	11.8
53	+37	5 −5 −1	200	168	11.3
54	+39	4 −2 −4	142	173	13.0
55	+41	5²−3 −1	213	178	11.7
56	+41	4 −5²−1	187	186	12.8
57	+41	4 −3²−4	167	194	13.9
58	+42	5²−5 −1	163	165	11.9
59	+43	7 −3 −2	177	168	11.7

TABLE III.—CONTINUED

NO.	AXIS DEVIATION	SOMATOTYPE	WT.	HT.	PONDERAL INDEX $\left(\frac{\text{HT.}}{\sqrt[3]{\text{WT.}}}\right)$
60	+43	3 –2 –5	170	181	12.8
61	+43	2 –4 –4	148	174	12.2
62	+43	5 –3 –2	186	175	12.1
63	+43	3 –6 –2	204	185	12.4
64	+44	4 –5 –2	174	168	11.8
65	+45	6 –3 –2	200	177	11.9
66	+46	4^2–3 –3	180	181	12.2
67	+46	2^2–3 –5	143	170	12.8
68	+47	6 –3^2–1	195	172	11.5
69	+47	2 –3^2–5	134	168	12.9
70	+48	5^2–4^2–2	177	172	12.0
71	+48	5 –2^2–4	151	169	12.5
72	+48	3 –4 –4	152	172	12.7
73	+49	4 –3 –3^2	178	177	12.4
74	+50	4 –4 –2^2	170	173	12.2
75	+50	4 –3 –3	178	176	12.3
76	+50	3 –5 –3	175	179	12.6
77	+52	5 –2 –3	191	188	12.8
78	+52	5 –3 –2	162	171	12.3
79	+53	5 –3 –2	154	169	12.4
80	+54	4 –3^2–4	163	170	12.2
81	+54	3 –3^2–4	165	179	12.8
82	+54	2 –3 –5	156	179	13.1
83	+55	5^2–4 –2	191	177	12.1
84	+55	5 –4 –1	174	171	12.0
85	+55	3 –5 –2	176	185	12.3
86	+55	2 –5^2–3^2	174	176	12.4
87	+56	3^2–3 –5	164	176	12.6
88	+56	2 –3 –5	133	166	12.8
89	+57	6 –3^2–1	158	164	11.8
90	+57	6 –3^2–1	188	176	11.9
91	+57	3 –4 –4	183	178	12.8
92	+58	4 –3 –3	175	179	12.6
93	+58	4 –3 –4	165	180	12.9
94	+59	4 –5 –2	182	181	12.8
95	+59	3 –4^2–3	157	175	12.8
96	+59	2 –3 –6	164	182	13.1
97	+59	1 –3 –6	170	195	13.8
98	+60	4 –4^2–2	184	178	12.3
99	+60	4 –3^2–4	157	173	12.6
100	+60	3^2–4 –3^2	172	178	12.6
101	+60	3 –4 –4	172	180	12.7
102	+60	2^2–4 –5	150	173	12.8
103	+62	6 –3^2–2^2	190	175	12.0
104	+62	2^2–3 –6	177	183	12.8
105	+62	2 –3 –5	136	165	12.6
106	+63	7 –3 –1	225	177	11.4
107	+64	5 –4^2–1	191	169	11.5
108	+64	5 –4 –2	170	176	12.5
109	+64	4^2–3 –3	153	164	12.1
110	+64	4 –3 –4	193	185	12.6
111	+64	4 –4 –4^2	155	174	12.7
112	+68	6^2–4 –1	210	178	11.7
113	+68	5 –4 –1	194	173	11.7
114	+68	4 –6 –2	220	182	11.8
115	+68	3 –5^2–1	186	176	12.1
116	+68	4 –4 –2	155	166	12.1
117	+68	2 –3 –6	157	184	13.4
118	+69	6 –3 –2	180	174	12.1

TABLE III.—CONTINUED

NO.	AXIS DEVIATION	SOMATOTYPE	WT.	HT.	PONDERAL INDEX $\left(\frac{\text{HT.}}{\sqrt[3]{\text{WT.}}}\right)$
119	+70	6^2–3 –1	190	172	11.8
120	+70	2^2–2^2–6	138	171	13.0
121	+71	2 –6 –1	177	171	12.0
122	+71	3 –4 –3	189	183	12.5
123	+72	4 –3 –4	176	180	12.7
124	+73	2 –3 –6	144	173	13.0
125	+75	3 –3 –5	158	179	13.0
126	+76	2 –3^2–5	156	177	12.9
127	+77	2^2–2 –6	136	181	13.8
128	+78	4 –5 –2	164	173	12.4
129	+80	3^2–5 –2	177	178	12.4
130	+82	5 –6 –1	177	172	12.0
131	+82	2 –4 –5	171	180	12.8
132	+82	1 –4 –5	179	190	13.3
133	+83	1 –3 –6	147	176	13.1
134	+85	3 –2 –5	144	169	12.7
135	+90	4 –6 –1	174	172	12.1
136	+90	2 –5 –4	161	172	12.4
137	+90	3^2–3^2–4	169	177	12.6
138	+90	3 –2 –5	188	194	13.3
139	+90	3 –2 –6	160	187	13.5
140	+90	2 –1^2–6	121	176	14.0
141	+90	1^2–2 –6^2	135	185	14.2
142	+94	2 –3 –6	154	179	13.2
143	+109	4 –4 –4	153	174	12.8
144	+110	5 –4^2–2	203	188	12.5

These correlations indicate (1) no significant correlation between axis deviation and (a) height or (b) sternal ensiform measurements; (2) moderately significant negative correlations ($p > 0.05$) between axis deviation and (a) chest depth and (b) chest ratio; (3) highly significant negative correlations between axis deviation and (a) chest width and (b) weight, and a highly significant positive correlation with ponderal index.

In Table II the highly significant negative correlation between axis deviation and endomorphy (obesity) and the highly significant positive correlation between axis deviation and ectomorphy (linearity) are what may be expected from the anthropometric data. Accordingly, it may be stated that with increasing obesity (not muscularity) the electrocardiographic axis tends to shift more toward the "left," while the more linear (thin) the individual is, the more the electrocardiographic axis tends to shift towards the "right" in the normal individual.

DISCUSSION

The coefficients of correlation presented in Tables I and II bear out the general concept that physical causes affecting heart position influence the electrocardiogram in regard to axis deviation as manifested by the QRS complex. It is interesting to note that the axis deviation is influenced more by the physical attributes in the horizontal plane than in the vertical plane. This is further

corroborated by the insignificant correlations between axis deviation and height, and sternal ensiform measurements, which represent vertical measurements. The only other measurable variable in this study which revealed no significant correlation is the mesomorphic component. This is further substantiated by the other significant correlations since no correlation would be expected in the individual who is predominantly muscular, other than the contribution of muscularity to the horizontal plane.

Chest depth and chest ratio (depth/width) show a significant negative coefficient of correlation ($p > 0.05$). These observations may be interpreted as meaning that the greater the chest depth in an individual, the greater the tendency toward left axis deviation; the resulting effect is probably due to the effect of the shape of the thoracic cage on the cardiac position.

The highly significant negative coefficients of correlation ($p > 0.01$) include weight, endomorphy (obesity), and chest width, and are interpreted by us as meaning that the greater the obesity (weight, endomorphy, and increased chest ratio) the greater the tendency toward left axis deviation. The reverse is also true, in that the greater the diminution of these measurements (weight, endomorphy, and chest ratio) the greater the tendency toward right axis deviation. This statement is supported by the highly significant positive correlation between axis deviation and (1) ectomorphy and (2) ponderal index (that is, the less compact an individual, the greater the tendency to right axis deviation).

The only procedure of vectorial relationships included in this study is the axis deviation or the two-dimensional configuration which is, in essence, the frontal plane projection. However, since the heart is considered to be a volume conductor, it is reasonable to suggest that by incorporating a third dimension or spatial configuration, it may be possible to report even higher and more significant correlations between body build and the heart position as determined by vectorial methods, which probably define more accurately the electrical potentials arising from the heart within the thoracic cage.[11]

With the technique of somatotyping, a more reliable index in body build is given for predicting axis deviation in a certain physique. Where somatotyping is not available, it is suggested that the ponderal index be employed in addition to the usual method of description of tall, short, medium, etc., or other criteria that cannot give a reliable index as to the physique. It is believed that by incorporating such data with the clinical description more accurate interpretations of the electrocardiographic pattern would be possible.

SUMMARY

1. Coefficients of correlation between measurable variables of physique and axis deviation are reported.

2. In the subjects studied, axis deviation is influenced more by horizontal configuration than by linearity. In general it may be stated that there is an association between the degree of "compactness" of the individual and the tendency to left axis deviation. In the absence of endomorphy (and perhaps mesomorphy), there is an association between the tendency to right axis deviation and the degree of ectomorphy of the subject.

3. Sheldon's index of body build is presented and offers a more satisfactory measurement in correlating axis deviation with structural variations.

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CHRONIC COR PULMONALE AS A COMPLICATION OF FIBROCYSTIC DISEASE OF THE PANCREAS

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IT IS generally recognized that right ventricular hypertrophy and congestive heart failure may result from chronic pulmonary disease. That such can occur in infancy and early childhood is not common knowledge. In order that the importance of the problem may be better appreciated, we are presenting two cases of fibrocystic disease of the pancreas with severe pulmonary pathology, occurring in young children, complicated by right ventricular hypertrophy and congestive heart failure, demonstrated at autopsy.

Fibrocystic disease of the pancreas has been recognized as a clinical entity since Andersen's description of the disease in 1938.[1] The etiology has been the subject of much study, and as yet there is not complete agreement among investigators. There have been two principal hypotheses advanced. The first theory proposes that a deficiency in the pancreatic secretions results in poor absorption of fats and the fat-soluble vitamin A and that the epithelial metaplasia, bronchiectasis, and bronchopneumonia result from vitamin A deficiency.[1] The second theory is that the pancreatic lesion is part of a systemic disease in which various organs may be involved, with the production of abnormally viscid secretions, causing dilatation and obstruction of one or several glandular structures.[2,3]

Usually no gross abnormality of the pancreas is noted. However, if marked cystic changes are present, the organ may have a furrowed appearance. On cutting the pancreas, it is found to be firm; occasionally calcifications are present, which produce a grating sound on section. Microscopically there is dilatation of the pancreatic ducts with inspissation of the secretion, atrophy of the acini, and replacement with connective tissue. The islands of Langerhans are normal. Obstruction of the bronchi by thick, tenacious, purulent sputum produces areas of hyperexpansion, atelectasis and lobular pneumonia. As the disease progresses, bronchiectasis and pulmonary abscesses are found. There is thickening of the bronchiolar walls and replacement of the alveolar structures with fibrous tissue. *Staphylococcus aureus*, resistant to penicillin, is usually the invading organism.

Because of the extensive destruction and alteration of the pulmonary parenchyma, it has been estimated that chronic cor pulmonale will occur in 70 per cent of infants and children dying from fibrocystic disease.[4] Until recently,

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however, few clinical observations have been made concerning this complication. Wiglesworth[5] quotes an unpublished case of G. L. Duff, in which cor pulmonale without histologic changes in the pulmonary vascular tree occurred. Andersen[6] states that persistent bronchitis with development of lung abscess and bronchiectasis or the occurrence of cor pulmonale secondary to the pulmonary changes remains the principal cause of death. Lowe[7] has stated that the development of right ventricular failure with anasarca is the least understood of the causes of death among these patients. May and Lowe[8] have reported six cases of cor pulmonale occurring after many months of severe dyspnea and cyanosis. Royce[4] has reviewed the subject of cor pulmonale in infancy and early childhood and has reported on twenty-five infants and children examined at autopsy with cor pulmonale associated with fibrocystic disease of the pancreas. Nine of these children were 1 year of age or younger, and the youngest patient of the series was 1½ months of age at the time of death.

Cor pulmonale may be defined as right ventricular hypertrophy with or without right ventricular failure, secondary to disease of the pulmonary parenchyma, primary disease or distortion of the pulmonary arteries, or deformities of the bony thorax, any of which can produce increased resistance to the flow of blood through the smaller vessels and capillaries coursing through the interalveolar septa. The term cor pulmonale should not be used to include right ventricular hypertrophy resulting from heart disease per se, for example, mitral stenosis, left ventricular failure, or congenital abnormalities. Emphysema has been shown to be the common pathologic pulmonary factor responsible for most of the cases of adult cor pulmonale.[4] The condition is well recognized as one of the less common types of heart disease in the adult, but it has been considered uncommon in infants and young children.

Cor pulmonale with right ventricular failure in combination with fibrocystic disease of the pancreas presents a problem in diagnosis. Prominence of the left side of the chest, when present, is an important positive diagnostic finding, indicating right ventricular hypertrophy. The cyanosis present may be due to the pulmonary pathology or to the cardiac failure, or to a combination of the two. Hepatomegaly may be the result of right ventricular failure, or it may be present with fatty infiltration of the liver, which occurred in nineteen of Andersen's forty-nine cases, or with cirrhosis of the liver, which occurred in four of these cases.[1] The liver may be displaced downward by the emphysematous lungs. In the more advanced stages of the disease, however, ascites and pedal edema occur with right ventricular failure. Lending support to the cardiac origin of the edema and ascites is the work of Lowe, May, and Reed,[9] who found the total serum protein level to be normal in the majority of debilitated patients with fibrocystic disease of the pancreas, who were studied.

The electrocardiogram frequently is not of help since it may show the normal right ventricular hypertrophy of infancy or the vertical position of the heart in an emphysematous chest. However, when right ventricular hypertrophy by electrocardiogram is present after the age of 6 months, it is of definite diagnostic value.

The x-ray examination of the chest is valuable in demonstrating right ventricular hypertrophy and prominence of the primary pulmonary artery, seen best with the patient placed in the right anterior oblique position. However, the roentgenologic findings are often not clear-cut, and the heart may actually appear small due to the downward displacement of the heart or to its compression, both resulting from emphysema. As Caffey has stated, hypertrophy without dilatation contributes little to the over-all size of the cardiac silhouette since the increased thickness in the ventricular wall is usually only a few millimeters.[10] Added to these limiting factors is the technical difficulty involved in the examination of an infant, often seriously ill and crying, and suffering with severe dyspnea and cough.

Because of these difficulties the definite diagnosis of right ventricular hypertrophy in this age group is made only by pathologic examination of the heart. Therefore, it is difficult to estimate the true incidence of the condition. White has stated that 3 mm. is the average thickness of the right ventricular wall in the adult,[11] and Mallory states that 5 mm. would constitute marked right ventricular hypertrophy in an infant or child.[12] Our cases satisfy the requirement for right ventricular hypertrophy by pathologic examination.

Control of the respiratory infection with antibiotics and chemotherapeutic agents is of utmost importance, and aureomycin has been most useful in this regard. Morphine should be avoided because of its depressant effect on the respiratory center with resultant decrease in elimination of carbon dioxide. It has been stated that specific therapy for the cardiac failure is ineffective, postponing death for only a matter of hours.[4] Although control of the pulmonary infection is urgent, we believe that digitalis, mercurial diuretics, salt restriction, and intravenous aminophylline are of more permanent therapeutic value in some patients. The good response to digitalis demonstrated in Case 2 is pertinent in this regard. Although digitalis was omitted on two occasions, nine months elapsed between the period of the first administration of the drug and the time of death.

CASE REPORTS

CASE 1.—J. E. R., a 20-month-old white boy, was apparently well until 8 months of age, at which time he began to have repeated episodes of fever, dyspnea, and cough productive of purulent sputum. Bronchoscopy was performed at that time in another hospital because aspiration of a foreign body was suspected; none was visualized, however. Prior to that time the patient has been constipated, but with the appearance of the respiratory symptoms his stools became greasy, malodorous, and bulky. Between the ages of 8 months and 20 months he lost 8 pounds, despite a good appetite. The child's mother had had two miscarriages and one stillbirth prior to the birth of the patient.

The child was first admitted to Emory University Hospital on Aug. 17, 1951, at the age of 20 months. The temperature was 100°F. rectally. Moist râles were present bilaterally. The roentgenogram of the chest on August 18 showed increase in the pulmonary markings bilaterally, more marked in the bases, representing bilateral chronic lung disease. A three-day stool specimen, weighing 100 grams, contained 60 grams of fat and 4.9 grams of nitrogen. The film test was negative for trypsin activity. Attempts to obtain duodenal contents for determination of trypsin activity were unsuccessful. The culture of the sputum yielded Pseudomonas.

The patient received aureomycin, 250 mg. three times a day for two days and then 100 mg. three times a day, pancreatin, U.S.P., 0.5 dr. three times a day, Sorlate, 0.5 Gm. three times a day,

and multiple vitamins. The temperature ranged between 99 and 101°F. throughout his hospital course. He was improved at the time of discharge on Aug. 24, 1951.

He continued aureomycin at home, but was readmitted to the hospital on Nov. 1, 1951, because of marked dyspnea and cough. His nutrition was remarkably good. The respiratory rate was rapid. The anterior-posterior diameter of the chest was increased. The apical cardiac rate was 200 per minute; the rhythm was regular. Pressure on the carotid sinuses did not influence the rate. No murmurs were heard. There were many large moist râles throughout both lung fields. The liver was palpable at the level of the umbilicus. There was mild cyanosis of the nose, fingers, and toes. There was a trace of pitting edema of the ankles. Examination of the blood revealed the hemoglobin to be 13.6 Gm. per cent., 4½ million red blood corpuscles per c.mm., 12,950 white blood cells per c.mm., with a normal differential count.

The roentgenogram of the chest on Nov. 1, 1951, (Fig. 1) revealed extensive bilateral pulmonary infiltrations of a patchy nature. There were changes suggestive of right ventricular hypertrophy.

Unfortunately the patient was so ill that attempts to obtain an electrocardiogram were technically unsuccessful. Only Lead I was obtained, showing right axis deviation.

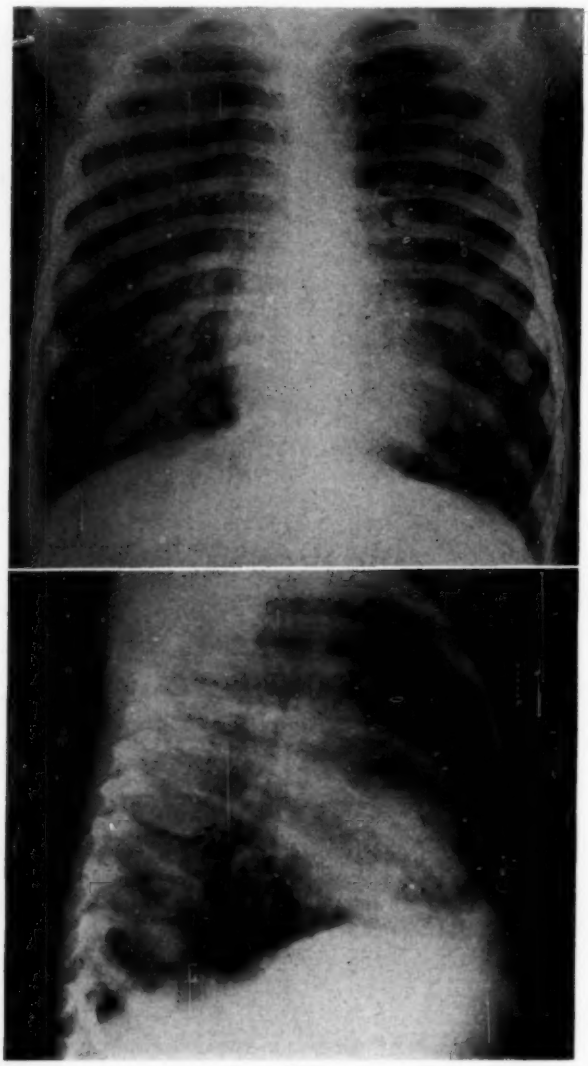
It was believed that cor pulmonale with right ventricular failure was present, secondary to the severe pulmonary disease. Penicillin, streptomycin, and aureomycin were administered. The patient was digitalized with lanatoside C, 0.4 mg. given in divided doses intravenously. He received aminophylline intravenously and rectally. A mercurial diuretic was given intramuscularly, and he was placed on a 200 mg. sodium diet. A marked diuresis occurred on the afternoon following the mercurial diuretic, and the patient showed marked temporary clinical improvement. However, the symptoms returned the following day and continued until his death. He was intermittently cyanotic. On Nov. 4, 1951, bronchoscopy revealed marked edema of the tracheobronchial tree, and a small amount of thick purulent material was aspirated. Following bronchoscopy polymyxin, 5 mg. every six hours intramuscularly, was administered. On the morning of November 5, coffee-ground vomitus, which was guaiac positive, was present. Abdominal distention without spasm was noted. He became progressively worse and died on Nov. 5, 1951.

Autopsy revealed four areas of intussusception in the jejunum, which apparently occurred as a terminal event. There were no areas of discoloration or perforation of the bowel. The heart weighed 71 grams, the normal weight being 56 grams. The epicardial surfaces were smooth and glistening and contained a moderate amount of bright yellow fat. There was slight dilatation of the cardiac chambers. The left ventricular wall measured 1.0 cm.; the right ventricular wall measured 0.7 cm. The left lung weighed 123 grams, with a normal weight of 74 grams. The right lung weighed 117 grams, the normal being 83 grams. The pleural surfaces were smooth and glistening. There was a doughy consistency of both lungs without crepitation. On cut surfaces thick, tenacious pus-filled bronchi and areas of early abscess formation were noted. The hilar and bronchial lymph nodes were enlarged. The pancreas weighed 19.8 grams and was markedly firm. No hemorrhagic areas were demonstrated. The liver weighed 450 grams, the normal being 370 grams. It appeared normal grossly. The gall bladder contained 5 ml. of thick, tenacious, cloudy, white material. There was marked congestion of the spleen.

Microscopic examination revealed some enlargement of the myocardial fibers with rounding of the nuclei. There was marked diffuse emphysema with occasional areas of atelectasis. Segmental pneumonia was present. The alveolar septa were thickened and were undergoing necrosis in many areas. The small bronchioles were filled with acute and chronic inflammatory cells and cellular debris. The mucosa of the bronchioles was absent in many areas and was undergoing necrosis in other areas. Surrounding many of the bronchioles were bronchiectatic abscesses. There was a striking increase in the fibrous tissue throughout the pancreas, destroying the normal lobular architecture. The acini were greatly decreased in number, and in many areas there was active necrosis of the acinar cells. The ducts were dilated and contained eosinophilic granular material, which was laminated in areas. The ductile epithelium was flattened in areas and was undergoing degeneration in others. Some of the islands of Langerhans were undergoing hyalinization with eccentrically placed nuclei. There was diffuse fatty metamorphosis of the liver with marked edema and congestion. Many of the bile ducts contained finely granular eosinophilic material.

The *diagnosis* at autopsy was fibrocystic disease of the pancreas with focal acute pancreatitis, bronchopneumonia with bronchiectatic abscesses, cor pulmonale, fatty metamorphosis of the liver, intussusception of the jejunum, terminal, and congestion of the viscera.

A.



B.

Fig. 1.—Frontal and lateral chest roentgenograms. There are extensive patchy pulmonary infiltrations and hilar adenopathy bilaterally. The configuration of the cardiac silhouette as seen in the lateral view (*B*) suggests right ventricular hypertrophy.

CASE 2.—G. E., a 27-month-old white girl, was first admitted to Egleston Hospital on Jan. 7, 1950, at the age of 7 months because of petechiae appearing the day before admission. Since birth the patient had had eight to twelve yellow, nongreasy stools daily, and frequent respiratory infections had been present.

The patient was a pale, normally developed infant, weighing only 11 pounds. There were numerous brown petechiae over the neck and trunk. Moist râles were present over both lung

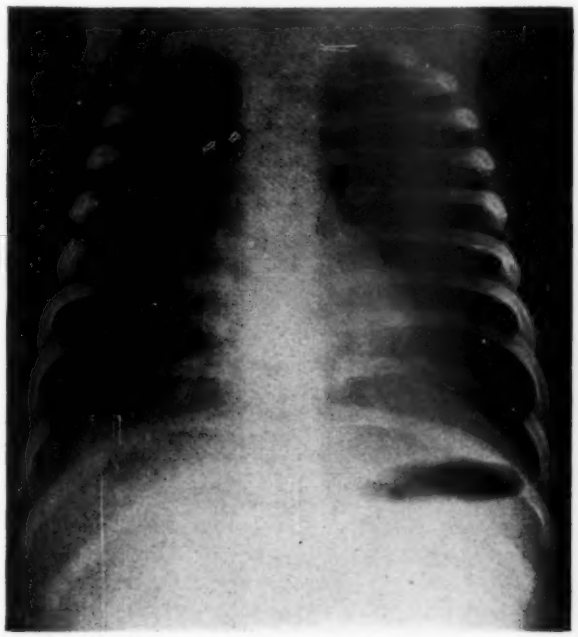


Fig. 2.—Chest roentgenogram of Jan. 16, 1950. Patchy pulmonary infiltrations are present bilaterally, more marked in the right base medially. The cardiac silhouette is normal.

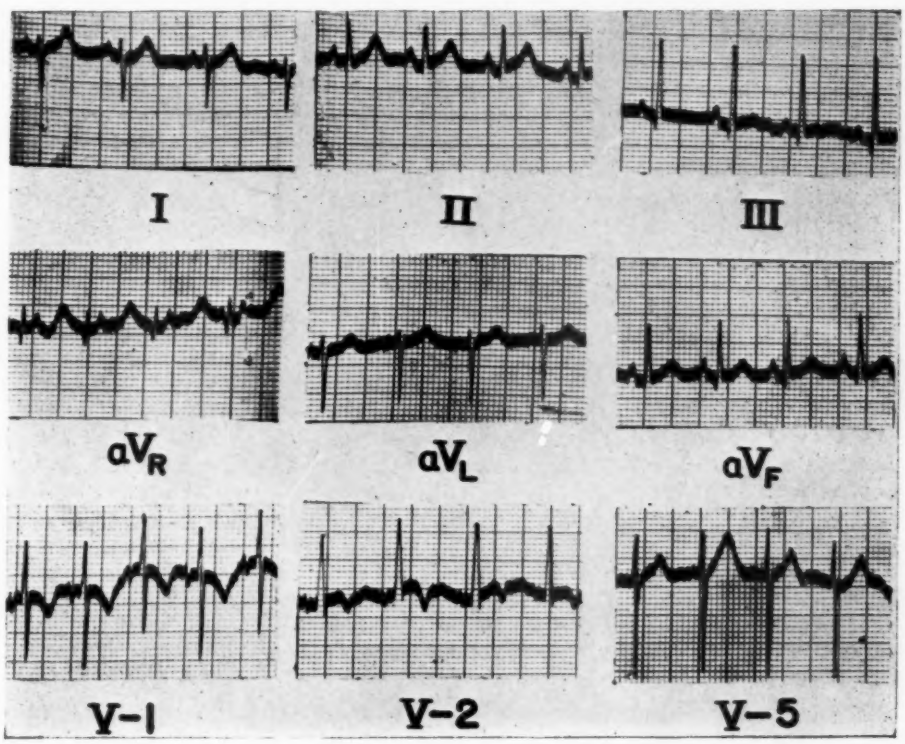


Fig. 3.—Electrocardiogram of Nov. 21, 1950, demonstrating right ventricular hypertrophy.

fields. The heart was normal in size to percussion. No murmurs were heard. The liver was palpable two fingerbreadths below the costal margin. There was no abnormality of the blood-clotting mechanism. Examination of the blood revealed the hemoglobin to be 9.5 Gm. per cent; red blood corpuscles 2½ million per c.mm.; white blood cells, 13,950 per c.mm., with 38 per cent segmented neutrophils, 61 per cent lymphocytes, and 1 per cent monocytes. The blood cholesterol was 165 mg. per cent. There was no trypsin activity of the duodenal contents or of the stool. A dried stool specimen weighing 100 grams contained 38.2 grams of fat. The fasting blood sugar was 90 mg. per cent. One-half hour after the ingestion of the glucose, the blood sugar was 240 mg. per cent; in one hour, 262 mg. per cent; in two hours, 232 mg. per cent; in three hours, 220 mg. per cent. Bromosulphalein test revealed 10 per cent retention of the dye forty-five minutes after injection.

The roentgenogram of the chest on Jan. 16, 1950, (Fig. 2) revealed the heart to be normal in size. There were increased vascular and peribronchial markings bilaterally. A liver biopsy on February 13 revealed fatty metamorphosis.

The petechiae cleared during the first three days, and the patient showed no further evidence of bleeding. She was given pancreatic granules, vitamins, penicillin, and a diet high in protein and carbohydrate and low in fat. She continued to have two to five grossly normal stools daily but improved clinically otherwise. At the time of discharge on March 13, 1950, instructions were given for her to remain on the above medications and to take sulfadiazine 0.25 Gm. twice daily.

On Nov. 9, 1950, her mother first noted cyanosis and edema of the eyelids. At the time of the second admission on November 12, her temperature was 100°F. The respiratory rate was rapid, and she had a mild nonproductive cough. There were fine moist râles throughout both lung fields. The heart was normal to examination. The liver was palpable 6 cm. below the right costal margin. There was moderate generalized edema. She was given aureomycin, penicillin, pancreatin, and oxygen without benefit. The electrocardiogram (Fig. 3) on Nov. 21, 1950, revealed the changes of right ventricular hypertrophy. Cardiac failure due to cor pulmonale was suspected, and the patient was digitalized. Following this medication, she improved rapidly. The liver decreased in size, and the edema disappeared. She improved sufficiently to be discharged on Dec. 10, 1950.

Following the second hospitalization, she had frequent respiratory infections with fever, cough, and cyanosis. She was admitted for the third time on March 30, 1951, and responded again to digitalis and oxygen. Antibiotics were also administered with benefit. The roentgenogram of the chest showed pulmonary congestion but did not differ otherwise from previous examination.

She was discharged for the third time on May 1, 1951, only to be readmitted five days later because of fever, cyanosis, and dyspnea. No improvement followed three days of intensive antibiotic therapy. The roentgenogram of the chest showed further increase in the size of the heart since the examination of April 10, and there was marked pulmonary congestion. Digitalis was again administered, and as before there was marked clinical improvement during the following week. In July, 1951, she developed generalized edema, and the liver was palpable three fingerbreadths below the right costal margin. Serum protein determination at this time revealed a total protein content of 7.3 Gm. per cent, with 5.0 Gm. per cent albumin and 2.3 Gm. per cent globulin. The fasting blood sugar was 65 mg. per cent. One-half hour following the intravenous administration of glucose the blood sugar determination was 213 mg. per cent; at one hour, 103 mg. per cent; at one and one-half hours, 58 mg. per cent; at two hours, 68 mg. per cent. The temperature ranged between 103 and 104°F. daily. Roentgenograms of the chest on July 18 (Fig. 4) and August 8 (Fig. 5) showed further increase in the size of the cardiac silhouette as compared with pictures made on Jan. 16, 1950, and May 7, 1951. Cortisone therapy was begun on August 9, but this had to be discontinued after three days because of increasing edema. On August 15 a mercurial diuretic was given with good response, but repeated diuretics were not of benefit. Marked ascites was present, and 250 ml. of clear yellow fluid was withdrawn from the peritoneal cavity. On Aug. 10, 1951 she began to have bloody bowel movements, and three days later she died.

At *autopsy* there was generalized anasarca. Two hundred ml. of yellow-tinged fluid was present in the peritoneal cavity, 100 ml. in the pleural spaces, and 75 ml. in the pericardial cavity. The heart weighed 150 grams, the normal being 57 grams. The anterior surface of the heart was formed largely by the right ventricle. The right atrium and right ventricle were dilated, and an

old thrombus, which was necrotic and purulent, was present in the right auricular appendage. The myocardium was paler than normal. The left ventricular wall measured 1.0 cm.; the right ventricular wall measured 0.6 cm. The left lung weighed 210 grams, and the right lung weighed 200 grams. The normal weights are 76 and 88 grams, respectively. The external surfaces of the lungs varied from white to purplish-red, the latter being rubbery in consistency. The bronchi contained small amounts of frothy material and large quantities of purulent material. The spleen

Fig. 4.

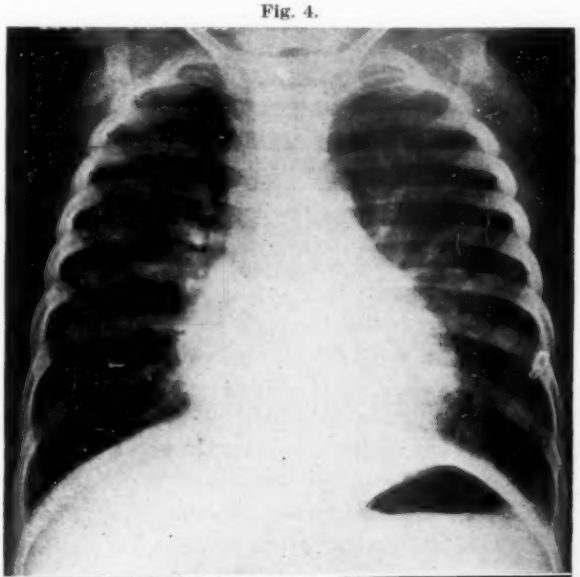


Fig. 5.

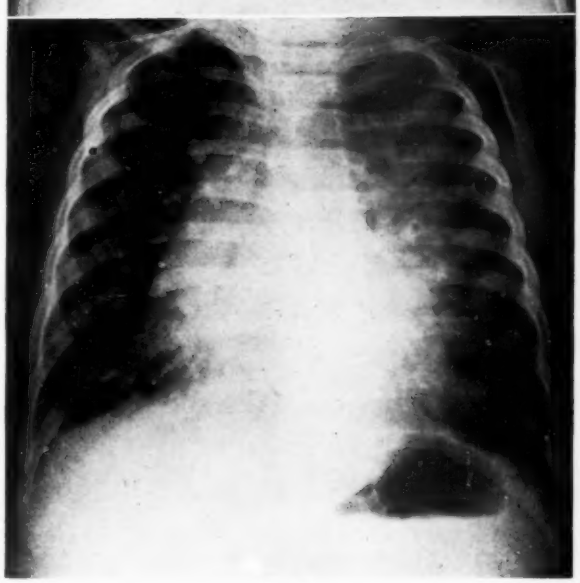


Fig. 4.—Chest roentgenogram of July 18, 1951. The pulmonary consolidations are now more widespread. The configuration of the heart suggests right ventricular hypertrophy.

Fig. 5.—Chest roentgenogram of Aug. 8, 1951, two days prior to death. The apparent mediastinal shift is due to rotation of the patient. The pulmonary infiltrations are more extensive than one month before.

weighed 50 grams, the normal weight being 35 grams. An ulcer measuring 1.7 cm. in length and 1.2 cm. in width was found on the posterior surface of the duodenum, adherent to the pancreas. The pancreas weighed 22.5 grams; it was firmer than usually seen, and the cut surfaces revealed a large amount of connective tissue stroma. The liver weighed 500 grams with a normal weight of 400 grams. Cut surface revealed a nutmeg appearance. The gall bladder contained 25 ml. of very viscid secretion.

Microscopic examination revealed tremendous hypertrophy of the individual fibers of the myocardium. There was marked bronchiectasis with many bronchiectatic abscesses. An interstitial pneumonitis was present. The alveolar walls were edematous and thickened. Many mononuclear phagocytes containing hemosiderin pigments were scattered throughout the parenchmya. Areas of pulmonary fibrosis were also present. Sections of the pancreas revealed tremendous cystic cavities composed both of large and small pancreatic ducts, many of which contained inspissated eosinophilic material. A few of the dilated pancreatic ducts showed moderate squamous metaplasia. The acini had been replaced by connective tissue. The islands of Langerhans were normal histologically. Fatty metamorphosis of the liver was present, most frequently seen in the central region of the lobules. There was some acute necrosis of the liver cells with definite deposits of connective tissue. Some of the bile ducts were distended with inspissated eosinophilic material. Cultures of the bronchial secretions yielded Proteus and Pseudomonas, and cultures of the blood yielded Pseudomonas. The diagnosis at autopsy was fibrocystic disease of the pancreas, bronchiectasis with abscesses, interstitial pneumonitis, cor pulmonate, fatty metamorphosis of the liver, and duodenal ulcer.

SUMMARY

There have been presented two cases of fibrocystic disease of the pancreas with associated chronic cor pulmonale and right ventricular failure, studied at autopsy. The difficulties in the diagnosis and the importance of the recognition of chronic cor pulmonale in the infant have been emphasized. Although the benefit from cardiac therapy in this condition may be limited, it should not be withheld or inadequately administered.

The authors wish to express their appreciation to Dr. Hines Roberts for his permission to report Case 2 and to Dr. J. Minor Blackford for the use of the electrocardiogram in this case.

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MULTIPLE ARTERIOVENOUS ANEURYSMS OF SOFT TISSUES AND BONE (PELVIS AND VERTEBRAE) RESULTING IN CARDIAC FAILURE

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NEW YORK, N. Y.

ABNORMAL anastamoses between the arterial and venous circulations may arise as the result of trauma or anomalous development. Most of these direct communications, regardless of etiologic background, do not affect profoundly the normal hemodynamic balance. Whether a vascular short circuit can be tolerated without measurable hemodynamic alteration is determined by the combined factors of displaced blood volume (a function of vessel diameter and magnitude of fistula) and duration of the communication. The volume of blood which passes through the fistula remains unavailable to the peripheral tissues. A critical stage is reached when homostatic compensation will require an augmented blood volume. If these crucial factors continue to exert their influence on the circulatory mechanics, more profound cardiovascular derangements ensue.

In most instances, the arteriovenous fistula is initially apparent. The resultant effects upon the heart appear only after a prolonged period and the causal relationship is quite evident.

A few cases occur in which the vascular short circuit remains hidden while its cardiac reflection commands the attention of the observer. Without an awareness of the underlying vascular shunt, and in the presence of cardiac enlargement and failure, and especially with hemodynamics suggesting aortic insufficiency, the diagnostic impression may be that of specific valvular disease or of an intrinsic cardiac anomaly.

A communicating vascular lesion located in a hidden recess of the body, and yet of sufficient magnitude to cause cardiac changes, can understandably present serious diagnostic problems.

The following case is reported because of such difficulties encountered during life and because of the remarkable and unique type of arteriovenous communication demonstrated at necropsy.

CASE REPORT

The patient was a 34-year-old white man, a veteran, who had led a physically active life, apparently with good stamina, until December, 1949. There was no previous known heart dis-

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ease, heart abnormality, arthritis, or chorea. He had a residual slight weakness of the left upper extremity and a slight left foot drop following an attack of poliomyelitis at the age of 8.

In December, 1949, he first noted dyspnea on exertion. Digitoxin administration was started at that time, followed shortly by salt-poor diet, ammonium chloride, and weekly injections of mercurial diuretics. By February, 1950, he developed orthopnea and ankle edema, and the frequency of mercurial injections was increased to three per week. On March 20, 1950, he was hospitalized. Information received from the hospital indicated that he had the symptomatology of left and right heart failure. A "to-and-fro murmur at the apex" and evidence of cardiac enlargement were noted. The pulse was 100; the blood pressure 140/70 mm. Hg. The diagnosis was "double mitral lesion with aortic insufficiency, etiology rheumatic fever." Treatment included a low-sodium diet and daily administration of mercurials, ammonium chloride, and digitoxin (0.2 mg.).

Upon transfer to the Veterans Administration Hospital on April 7, 1950, admission examination revealed a patient showing slight dyspnea, orthopnea, and cyanosis at rest. The neck veins were distended. The lung fields, examined in the sitting position, were normal. The heart was enlarged. There was no thrill. The rhythm was totally irregular with superimposed runs of coupling. The first apical sound was slightly loud. The second sound at the base was of normal intensity, but of poor quality. The second pulmonic was louder than the second aortic sound. There was a moderate, medium-pitched, harsh systolic murmur at the base, maximally at the third left intercostal space. *No diastolic murmur* was heard. The rate was 80 per minute without pulse deficit. The blood pressure in the upper extremities was 130/40-0 mm. Hg, and there was marked Corrigan's pulse. The femoral pulses were equal and good. There was moderate ascites, moderate hepatomegaly, slight splenomegaly, and marked dependent edema. There was slight weakness and diminution of deep tendon reflexes in the left upper and left lower extremities. No other abnormalities were detected. The admission diagnosis was inactive rheumatic heart disease, aortic stenosis and insufficiency, and mitral stenosis and insufficiency.

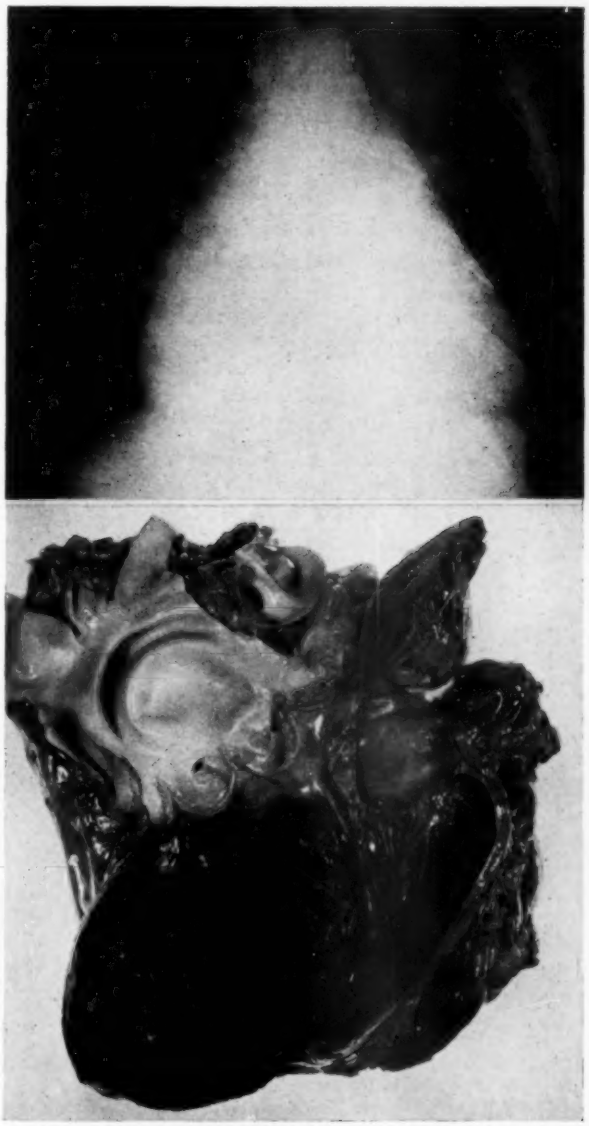
The electrocardiogram showed auricular fibrillation, runs of bigeminal rhythm, and nonspecific S-T and T wave abnormalities. The blood pressure fluctuated to 170/30 mm. Hg. The failure to detect a murmur of aortic insufficiency in the presence of a high pulse pressure and collapsing pulse suggested the possibility of an arteriovenous fistula. Auscultation over the entire body revealed murmurs just to the left of the first lumbar vertebra, posteriorly, and over the left pelvis, posteriorly. The murmurs were synchronous and of like quality. They were loud, harsh, blowing, continuous, diphasic, with greater amplitude in the systolic phase. The peak of the systolic phase occurred approximately at the time of the second cardiac sound. Chest roentgenograms revealed generalized cardiac enlargement and marked pulmonary congestion (Fig. 1,*A*). Roentgenograms of the spine and pelvis revealed a lytic lesion in the left pedicle of the first lumbar vertebra and mixed lytic and blastic lesions in the left sacrum and ilium, (Fig. 1,*B*). The clinical radiologic impression was that these lesions represented angiosarcomata resulting in arteriovenous fistulas.

The patient was treated with bed rest, salt-poor diet, oxygen and sedation, and maximum tolerated dosage of digoxin. During the first two weeks, he gained 8 pounds in weight and the signs of heart failure, including râles, increased. Four injections of Thiomerin were without effect. Urine specific gravities ranged from 1.010 to 1.012. Serum studies revealed: Na 104 meq./L., Cl 60 meq./L., CO_2 24 meq., blood urea nitrogen 23 mg. per cent. On a free fluid intake, he was given 45 Gm. of NaCl orally over a four-day period. He gained 3 more pounds in weight and the râles increased. Since his urinary output had been consistently greater than 1,000 c.c. per day, he was then restricted to 1,000 to 1,200 c.c. of daily fluid intake, and was given 128 Gm. NaCl orally over a nine-day period. This resulted in a 25-pound weight loss and concomitant improvement in his clinical status, an increase in serum Na to 134 meq./L. and Cl to 89 meq./L., and a progressive increase in urine specific gravity to 1.019. An injection of Thiomerin then produced an additional 6-pound weight loss and an elevation of urine specific gravity to 1.025.

Despite these results, his cardiovascular status could not be improved sufficiently to permit explorative surgery. The patient died five weeks after admission.

Post-mortem Examination.—The body was that of a well-developed and well-nourished white man of 34 years. There was bilateral ankle edema, and cyanosis of the lips and nail beds. The extremities were symmetrical. The pericardial cavity was obliterated by numerous fibrous and fibrinous adhesions. The pleural and peritoneal cavities were unaltered. The right lung weighed 1,150 grams; the left lung weighed 800 grams. Section of the lungs revealed massive edema.

A.



B.

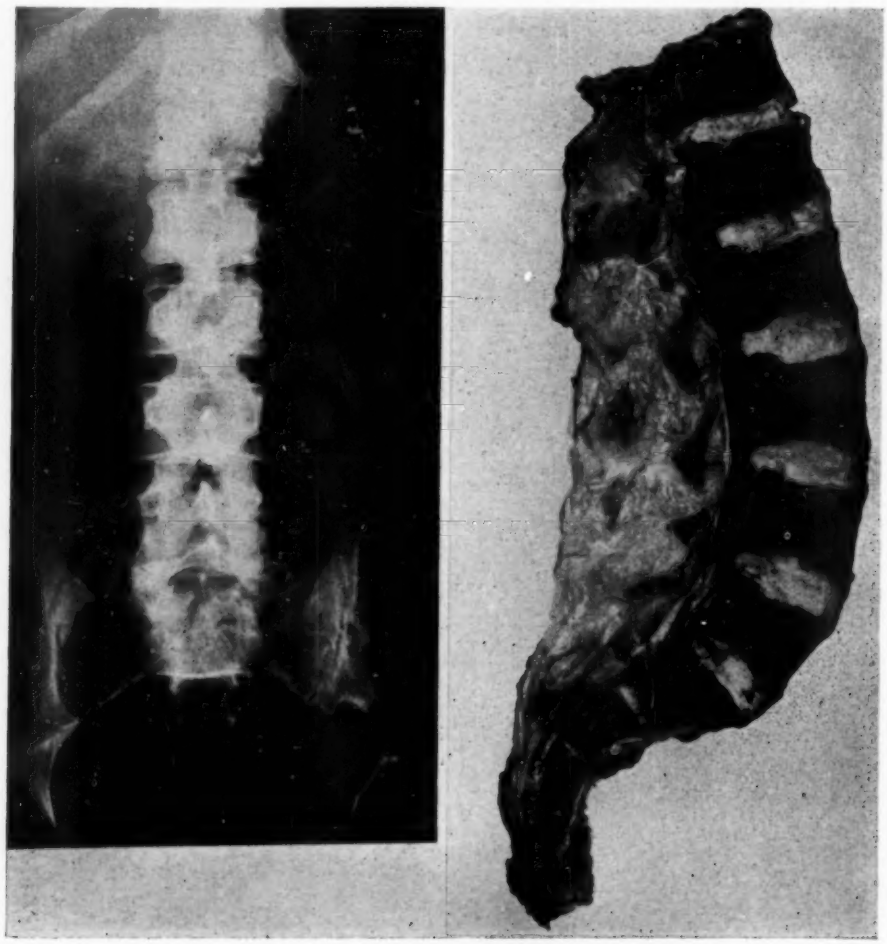
Fig. 1.—*A*, Roentgenogram of the chest. The heart is enlarged in all diameters, which, with the evident pulmonary congestion, suggests old rheumatic heart disease.

***B*, Heart showing only myocardial hypertrophy.**

The heart weighed 1,300 grams (Fig. 2,*A*), and was greatly enlarged in all dimensions. The valvular orifices were dilated. The following were their circumferential measurements: aortic 8.4 cm., pulmonary 9.4 cm., mitral 14 cm., and tricuspid 16 cm. The valve leaflets were thin,

translucent, and pliable. The right ventricular wall measured 1.2 cm. in thickness; the left ventricular wall measured 2.2 cm. in thickness. The myocardium disclosed no abnormalities other than hypertrophy. The endocardium was smooth and glistening. The coronary arteries were patent and showed no atherosclerosis. There were no abnormal communications between the right and left sides of the heart.

The aorta was normal. Both common iliac arteries were of equal diameter. The left hypogastric artery branched from the left common iliac artery normally, and in its course inferiorly suddenly widened to form a fusiform aneurysm. There was moderate atherosclerosis within this



A. *B.*

Fig. 2.—*A*, Roentgenogram of the spine and pelvis. Note the mixed blastic and lytic lesions in the left ilium and sacrum, and the lytic area in the left pedicle of the first lumbar vertebra.

***B*, Sagittal section of the spine and pelvis. The vascular spaces in the sacrum and in the first lumbar vertebra are evident.**

aneurysmal portion. The inferior vena cava was dilated. The left common iliac vein was larger in diameter than the one on the right. At a point about 6 cm. beyond the bifurcation of the inferior vena cava, the left common iliac vein was considerably dilated to form a loculated aneurysm which occupied the major portion of the posterior pelvic cavity (Fig. 3). The arterial and venous aneurysmal masses communicated through an aperture which measured about 1 cm. in diameter. The intimal edges of this arteriovenous fistula were smooth and directly continuous with smooth

intima on either side. At a point opposite the venous side of the fistula there were a number of discrete calcific atheromatous plaques. In addition to the larger arteriovenous communication, there were a number of small adjacent connecting channels, none of which measured more than 2 mm. in diameter. An injection of dye demonstrated the patency of these minor shunts. Farther posteriorly, the aneurysmal mass continued as loculated and dactylate extensions into the soft tissues of the pelvic concavity, and thence into the substance of the underlying bony structures. The largest of these extensions was noted in the region of the left sacroiliac joint which had been destroyed extensively. Numerous other gross ramifications extended into the left iliac bone, the sacral vetebrae, and the superior portion of the coccyx (Fig. 2,*B*). These intraosseous channels were lined by smooth intima, and were not thrombosed. A similar loculated mass of blood channels occupied the left posterior and lateral portions of the body of the first lumbar vertebra with destruction of the left lateral process. No communication could be demonstrated between the vascular mass in the first lumbar vertebra and the aneurysms within the pelvic cavity and bones. No other vascular abnormality was noted elsewhere in the body.

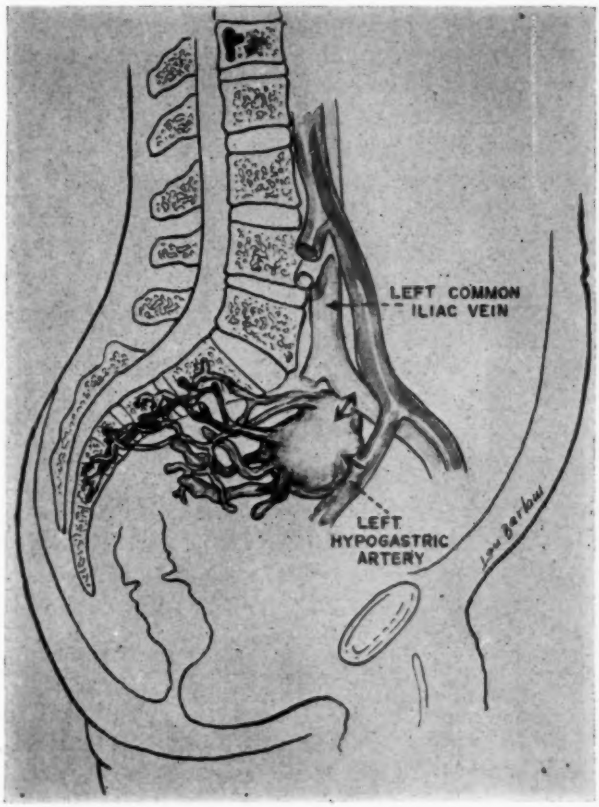


Fig. 3.—Diagrammatic representation of the arteriovenous aneurysm, showing the extensions into the pelvis and pelvic bones. Note the isolated lesion in the first lumbar vertebra.

Other anatomic post-mortem findings including a moderate cardiac cirrhosis and extensive visceral passive congestion.

Microscopic Examination.—Sections of the heart disclosed hypertrophy of the myocardial fibers with rare focal zones of myomalacia. The valves, endocardium, and coronary arteries were normal. Sections of the kidneys disclosed severe congestion. The renal arteries were free of sclerotic changes.

The sections taken from the arteriovenous communication and aneurysms disclosed the following (Fig. 4,*B*): The orifice rim between the aneurysms of the left hypogastric artery and

the left common iliac vein showed a continuity of the intima and the subintimal layers of these vessels. Elastic tissue stains revealed an elastic layer to continue somewhat beyond the point of the presumed arteriovenous junction. The elastic stains of various segments of the large, thin-walled sac demonstrated the irregular presence of an elastica represented as an atrophic tortuous line. Sections through the minor shunts showed a profusion of dilated veins and arteries, the former characterized by prominent muscular walls. Sections of the osseous extensions of the aneurysm revealed dilated (Fig. 4,*A*), mature vascular channels, which followed an irregular course through the cortical and cancellous bone. These vessels showed the presence of an elastic layer. No direct arteriovenous communication within bone was visualized. One section from the sacrum showed foci of profuse capillarization.

The histologic examination of tissue from other organs confirmed the gross diagnoses.

DISCUSSION

In the absence of other lesions in this case, the massive arteriovenous communication must be considered the precursor as well as instigator of the cardiac hypertrophy and cardiac failure. Arteriovenous aneurysm as a cause of heart disease is a common clinical phenomenon. Probably in every instance there is some cardiovascular effect, and yet only occasionally can this be estimated. The synergistic factors of displaced volume and time will determine whether this effect will eventuate in perceptible systemic change.[1] Varying proportions of these two elements will create widely varying clinical pictures. One extreme is represented in the case reported by Danaraj[2] in which a traumatic aneurysm ruptured into the vena cava causing acute cardiac failure and death within thirty hours. Mason[3] described a case of traumatic arteriovenous fistula of the left subclavian vessels in which extreme cardiac decompensation occurred nine weeks after the inception of the fistula. In those instances where the fistula is small, a proportionately longer interval is required before cardiac changes are manifest. The femoral aneurysm in Reid's case,[4] for instance, was of seventeen years' duration before cardiac enlargement was evident.

Two factors, decreased coronary blood flow and increased cardiac output, have been invoked to explain the cause of the cardiac effect of arteriovenous fistulas. Lewis and Drury,[5] in five patients with acquired arteriovenous fistulas, could find no venous pressure changes. They assumed, therefore, that the cardiac output was normal. Study of peripheral arterial flow suggested the presence of decreased coronary artery flow, which they assumed to be the probable cause of cardiac enlargement. However, subsequent studies[6] by direct cardiac catheterization in patients with acquired arteriovenous fistulas have demonstrated increased cardiac output and have shown that the changes in peripheral arterial flow are probably largely neurogenic. Two mechanisms causing increased cardiac output in arteriovenous fistulas are: (1) increased pulse rate compensating for the fall in blood pressure caused by the fistula (Marey's reflex); and (2) increased central venous pressure resulting from shunting of blood directly to the venous side of the circulation (Bainbridge reflex). Other evidence[5,6] indicates that the Marey's reflex is the more important factor.

To determine the etiology of the arteriovenous fistula in the present case several considerations must be examined. There is a threshold of tolerance to a shunt before progressive changes occur. If it is assumed that this lesion is

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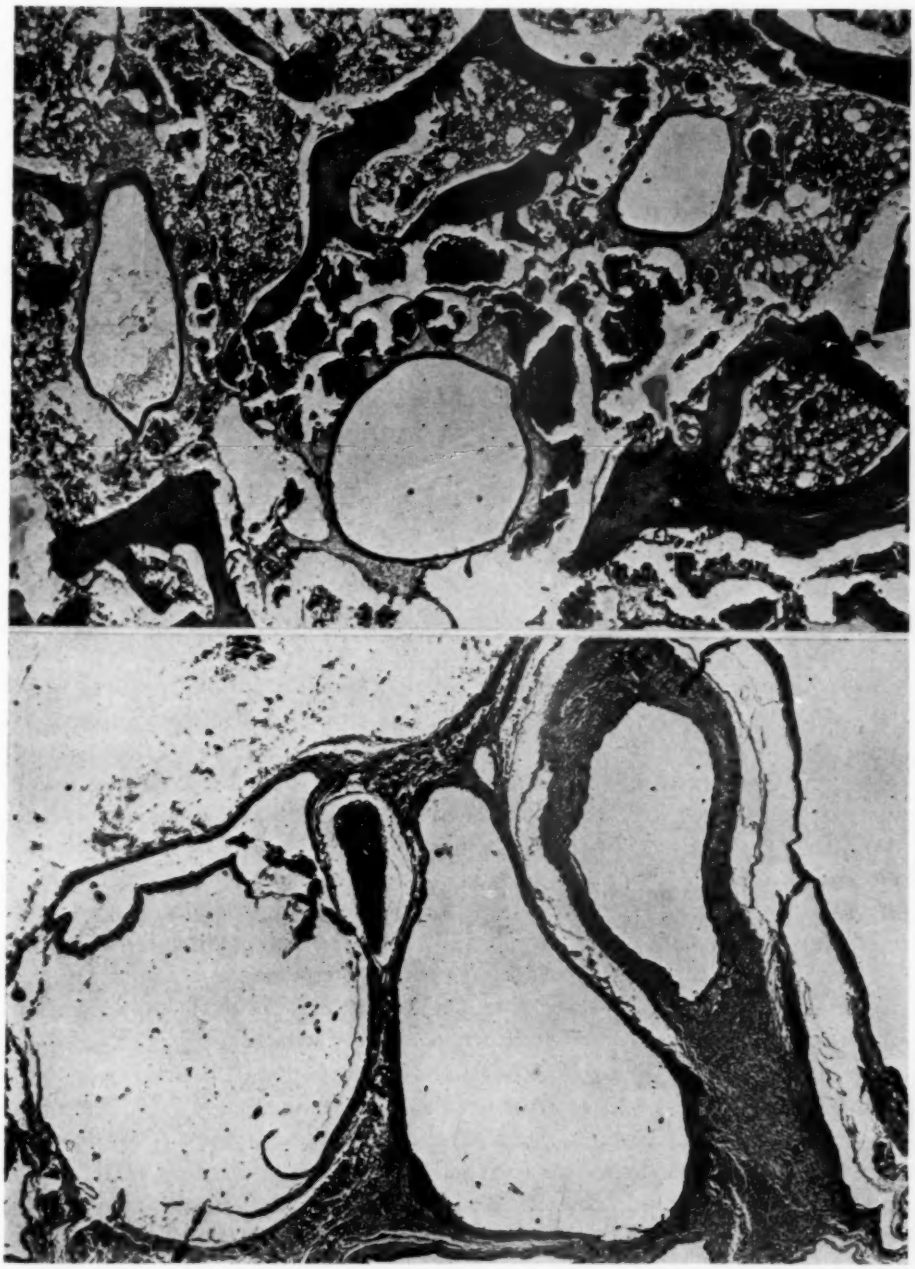

B.

Fig. 4.—*A*, Photomicrograph of sacrum showing dilated mature vascular channels permeating the bone. (H&E × 40.)

B, Photomicrograph of soft tissues of the pelvis showing mature arterial and venous components of the aneurysm. (H&E × 40.)

of congenital origin, it is difficult to understand why this formidable aneurysm which terminated in striking cardiac hypertrophy and fulminating decompensation failed to manifest its presence during childhood, an active military career, and manual labor of adult life. Indeed, the startling transformation from unlimited compensation to rapid cardiac failure in the face of all therapeutic measures would rather suggest a recent, traumatically induced arteriovenous fistula. Trauma was the cause in 85.7 per cent of arteriovenous aneurysms in Callander's large series.[8] Goldberger[9] states that enlargement of the heart usually does not occur in congenital fistulas, a view shared by Seeger.[10] Holman,[11] on the other hand, declares that the physiologic effects of congenital communications differ in no respect from those found in the presence of acquired communications, except in degree. In a series of nine cases of congenital arteriovenous fistulas described by Pemberton and Saint,[12] three cases had cardiac enlargement. In Ward and Horton's[13] series of forty-four congenital arteriovenous fistulas (all under 15 years of age), two patients had cardiac enlargement.

The evidence of intimal continuity between the arterial and venous components is of no assistance in determining the etiology. Matas[14] has observed that margins of the arteriovenous orifice are covered by endothelium directly continuous with the endothelium of the communicating vessels after a period of six to eight weeks' duration.

Factors which favor the impression of a congenital origin are: (1) there is no history of injury; (2) there are no gross or microscopic features to indicate traumatic intervention; (3) the site of this aneurysm is an unlikely site of trauma; (4) the considerable size of the aneurysm, the attenuation of the walls, and the patchy calcific atherosclerosis of the venous sac, all suggest a long-standing process; (5) there are multiple discrete communications between the involved artery and vein (considered the typical feature of congenital arteriovenous fistulas by Rienhoff[15]); (6) it is difficult to distinguish artery from vein even with elastic tissue stains (this development of a perceptible elastica in involved veins has been noted in visceral[8,10] and cerebral[16] fistulas of long duration, and has been termed "arterialization" by Carrel); (7) there are posterior extensions of the aneurysm into the pelvic bones where they form complex sinusoidal cavities; and (8) there is an isolated congeries of vessels in the first lumbar vertebra, with no apparent continuity with the vascular mass in the sacrum.

An arteriovenous communication within the substance of bone is an extremely rare occurrence. Case 31 in Reid's series[17] was a 35-year-old woman who presented signs and symptoms of an arteriovenous aneurysm in the right tibial region. The amputated specimen revealed massive involvement of the tibia by mature vessels. The author considered the circulatory communication to be within the bone itself. The extraordinary intraosseous lesions in this case are similar to those in Reid's case. It should be noted, however, that Reid described aneurysmal arteries entering and veins leaving the bone, with no demonstrable fistulas outside the bone. The question arises as to whether the intraosseous defects in the present case can be considered to have resulted from a retrograde dilatation of the tributary veins draining the pelvic bones. The factors militating against this explanation are: (1) there was no demonstrable

aneurysmal communication within the similar osseous lesion in the first lumbar vertebra; (2) the dilated vessels communicating between the bones and the venous side of the aneurysm were much more numerous than the tributaries which normally enter the common iliac vein, and (3) there was no similar aneurysmal dilatation of the other tributaries of the iliac veins.

The extension of the aneurysms into bone suggests a qualitative relationship to the aneurysmal bone cysts described by Lichtenstein.[18] The lesion he described, however, consists of a solitary fibrous process permeated by an enormously dilated plexiform vascular bed. An anomalous arteriovenous aneurysm was entertained as a possible basis for this vascular disturbance. The histologic picture of the aneurysmal bone cyst consisting of pools of blood in markedly dilated preformed vascular channels bordered by a supporting connective tissue matrix in which there is hemorrhage, giant cell reaction, and reparative new bone formation bears only slight, if any, resemblance to this case. Here, the vessels within bone form a distinct network of well-formed arteries and veins, with practically no hemorrhagic, fibrous, or giant cell reaction about them. In addition, we have in this case a definite arteriovenous aneurysm of large vessels, which in Lichtenstein's cases was only a theoretic possibility. Moreover, none of his cases showed any systemic reflection of an abnormal vascular communication.

A clinical picture which bears a resemblance to the present case is seen in a significant number of cases of generalized Paget's disease of bone. Cardiac hypertrophy and high cardiac output in the face of heart failure of arteriovenous origin had prompted Edholm, Howarth, and McMichael[19] to investigate the osseous blood flow in Paget's disease. Their studies disclosed a remarkable increase in the amount of blood flowing through diseased bone, often twenty times normal. They concluded that the progressive alteration in osseous structure had permitted the development of enormous numbers of arteriovenous fistulas, the cumulative effect of which was sufficient to cause cardiac failure.

The evidence at hand indicates that the vascular lesion in our case is congenital in origin. One has to assume that potential communicating channels were always present but expanded to a functional degree during the patient's adulthood. Reinhoff's review of congenital arteriovenous fistulas[15] emphasizes the fact that many congenital lesions of this variety do not become clinically evident till after puberty. A similar comment was made by Holman[11] in discussing congenital intracerebral arteriovenous aneurysms. The question as to why these channels abruptly dilated after three latent decades remains unanswered.

An interesting aspect of this case was the extraordinary hyponatremia and hypochloremia. This patient did not present the usual clinical manifestations of a low-salt syndrome. This syndrome was suspected because of the history of prolonged salt deprivation and mercurical administration, and because of the lack of response to further mercurials. Contrary to the usual finding of oliguria,[20,21] this patient maintained an excellent urinary output, but manifested an inability to concentrate the urine. It was found, as in previously reported cases,[20,21] that hypertonic saline (in this case, orally) was necessary to correct the disturb-

ance and to promote diuresis. With treatment, the ability to concentrate urine and the response to mercurial diuretics returned to normal.

SUMMARY

A case is presented of a 34-year-old man who was hospitalized because of a three-month history of dependent edema and orthopnea. A diagnosis of rheumatic valvulitis was entertained, based upon the patient's age, the obvious signs of right and left heart failure, and a high pulse pressure. The absence of a murmur of aortic insufficiency in the presence of Corrigan's pulse prompted the consideration of arteriovenous fistula. Murmurs were heard in the lower vetebral and posterior pelvic regions and x-ray examinations of these areas revealed numerous lytic lesions. The coincidence of the pelvic murmurs and osseous lysis led to the clinical diagnosis of angiosarcoma with arteriovenous fistulas and resultant heart failure. An unusual low-salt syndrome, owing to salt deprivation and mercurial diuretics, was present. He expired five weeks after admission.

Autopsy disclosed an extraordinary cardiac hypertrophy and multiple communications between the left hypogastric artery and the left common iliac vein. A very large aneurysmal sac was found occupying most of the posterior pelvic cavity. Extending posteriorly were dilated vessels which entered the pelvic and vertebral bones to form loculated, interconnected, intraosseous vascular channels. Evidence is presented which suggests that these vascular lessions are developmental anomalies.

When one recalls that arteries and veins have a common embryonic origin from a capillary plexus, lying in close proximity to large vascular trunks, it is quite surprising that abnormal vascular communications do not occur more frequently. An alertness to this possibility may prompt the more frequent discovery of deeply hidden arteriovenous fistulas in those cases of decompensated heart disease in which the physical signs do not explain adequately the clinical findings.

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ARTIFACTS IN MULTIPLE CHANNEL ELECTROCARDIOGRAPHS USING A COMMON CENTRAL TERMINAL

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IT IS well known that the amplitude of an electrocardiographic deflection registered on a string galvanometer decreases with increasing electrode and skin resistance.[1] In this case the amplitude of the standardization potential shows a corresponding decrease, so that the true amplitude can be restored by adjusting the string tension and sensitivity. In amplifier electrocardiographs, whose input resistance is hundreds of times higher than that of string galvanometers, the amplitude of a deflection is practically independent of the skin resistance, so that the same sensitivity can be used in all leads. This permits registration of electrocardiograms without a thorough and time-consuming preparation of the skin, and even makes the use of dry electrodes possible.[1] However, during work with a well-known multiple-channel amplifier electrocardiograph it became apparent that the voltage of the electrocardiographic waves became progressively smaller during electrocardiographic observations of long duration, which led to drying of the electrode paste and thus increased the electrode resistance. Furthermore, it was found that even with freshly applied electrodes the voltage of the electrocardiogram was about 15 per cent lower than in single-channel electrocardiographs. In all these cases the standardization potential remained of normal amplitude. A further incomprehensible observation was that if one of the electrodes became disconnected, the leads which contained this electrode continued to show electrocardiographic deflections. In order to clarify these observations the circuit of the electrocardiograph was studied and additional experimental observations were made.

The electrocardiograph in question was constructed to allow any one of the standard and augmented unipolar limb leads or the central terminal leads to be registered on each one of its channels, independently of the other channel. To reduce the short-circuiting effect of the central terminal circuit, resistors of 0.1 megohm are used instead of the conventional 5000 ohm resistors[2]; the central terminal circuit (*V*) is left permanently connected to the right arm (*R*), left arm (*L*), and left leg (*F*) cables (Fig. 1). In addition, the aV terminals aV_R, aV_L, and aV_F are also permanently connected across each standard limb lead: these terminals also contain resistors of 0.1 megohm. The standardization circuit in each channel consists of a 1177 ohm resistor, both ends of which are connected through 0.6 megohm resistors to a common Weston mercury cell, which supplies a voltage of 1.019 V.

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It may be seen in Fig. 1 that the following short circuits are present in any given standard limb lead (for example, Lead I): Circuit $R\text{-}a\,V_F\text{-}L = 0.2$ megohm, corresponding to a conductance of 0.5 micromho. Circuit $R\text{-}V\text{-}L = 0.2$ megohm = 0.5 micromho. Circuit $R\text{-}a\,V_L\text{-}F\text{-}a\,V_R\text{-}L = 0.4$ megohm = 0.25 micromho. In the case of Lead I, the standardization cell is connected to R through a total resistance of 0.15 megohm, to L through 0.3 megohm, making a total resistance of 0.45 megohm and a conductance of 0.23 micromho. The combined conductance of the shunts equals 1.48 micromhos, corresponding to a resistance of about 68,000 ohms. If the skin resistance is reduced to a minimum of 2000 ohms by considerable rubbing, this short circuit will produce a fall of voltage of about 3 per cent in the electrocardiogram but, if the preparation of the skin is only cursory, the skin resistance may exceed 10,000 ohms and the drop of voltage will exceed 15 per cent. Contrary to the string galvanometer, this decrease of voltage is not accompanied by a corresponding decrease in amplitude of the standardization potential.

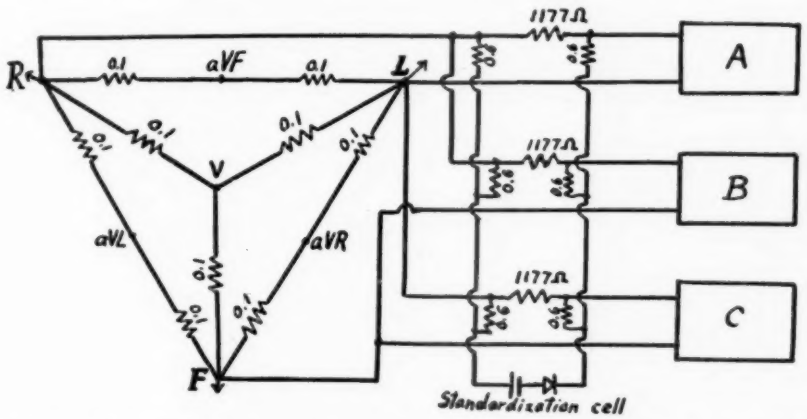

Fig. 1.—Circuit diagram of the connections between the three limb terminals R, L, and F and the amplifiers A, B, and C, during registration of the three standard limb leads. The values of the resistors are expressed in megohms except when designated. (See text.)

Fig. 2,*a*, is an electrocardiogram taken with dry electrodes; the height of the R wave in Lead II is 0.7 mv when compared with the 1.0 mv standardization potential. In addition, Lead III shows a wide S wave as an artifact due to skin polarization.[1] In Fig. 2,*b*, paste was applied to the electrodes, with only the slightest rubbing. The voltage of R_{II} is now 9.0 mv and the polarization artifact in Lead III is scarcely visible. In Fig. 2,*c*, finally, the skin was rubbed thoroughly with the electrode paste; the voltage of R_{II} is now 1.3 mv. Deficient preparation of the skin or drying of the electrode paste thus resulted in an apparent decrease in the electrocardiographic potentials of almost 50 per cent. Due to efficient elimination of A. C. interference, this decrease was not accompanied by the usual increase of superimposed 60 cycle oscillation and thus could not have been detected at all by the operator.

In Fig. 2,*d*, the right arm electrode was disconnected. In all single-channel electrocardiographs this would have caused disappearance of all electrocardiographic deflections in Leads I and II, and appearance of extreme A. C. interference. Actually, these leads showed no A. C. interference and continued to show electrocardiographic waves which, however, showed considerable change in their configuration. Study of the circuit diagram in Fig. 1 shows that when the right-arm electrode becomes disconnected, the corresponding amplifier wire

still remains connected over equal resistances to the *L* and *F* electrodes; its potential becomes equal to the average of their potential. Lead II is then equal to one-half the true Lead III while Lead I is the reverse of Lead II. Lead III is not affected. This is actually the case in Fig. 2,*d*. When the left-arm electrode is disconnected (Fig. 2,*e*), Lead II remains unchanged. The potential of the *L* cable is reversed, as it is now connected to the *R* and *F* electrodes; this causes Leads I and III to become identical and equal to one-half of Lead II. If the foot electrode is disconnected (Fig. 2,*f*), Lead I is not modified, but the *F* cable is now at a potential halfway between *R* and *L*. Consequently, Lead II becomes equal to one-half of the true Lead I and Lead III is the reverse of Lead II.

If one of the electrodes becomes disconnected in a single-channel electrocardiograph, the two standard limb leads containing this electrode will not show any electrocardiographic deflections and no standardization potential (or only a single spike instead of the usual square wave), and the tracing will contain extreme A. C. interference.[1] In our case these leads continued to register an electrocardiographic curve, were free of A. C. and showed a normal standardization curve. A similar finding was described[3] in multiple-channel electrocardiographs which did not use a central terminal but contained a capacitative coupling to the electrocardiograph frame, which in turn was connected to the patient's right leg. In this case the tracings contained a characteristic slow artifact at the end of QRS.[1] In our case, inspection of the standard leads thus could furnish no clue as to whether or not an electrode had become disconnected. To be sure, the unipolar limb lead from the disconnected electrode showed no electrocardiographic deflections. However, if the electrode was not completely disconnected but only showed considerable increase in resistance due to drying of the electrode paste, even the unipolar lead from the electrode in question showed only an inconspicuous decrease in voltage and could not be used to recognize the changes of configuration of the electrocardiograph as an artifact.

Several methods could be applied to remedy the situation:

1. The electrocardiograph could be used in its present form if considerable time is spent in thorough rubbing of the skin, if electrode paste is replenished at regular intervals during tests of long duration, and if the cable connections are checked carefully before registration of each electrocardiogram. Use of large-size electrodes (about 5 by 10 cm.) would decrease the skin resistance many times and thus minimize the artifacts described above.[1]

2. The circuit could be left in its present form, but the value of the resistors in the V and aV terminals could be increased to, let us say, 0.5 megohm. This would reduce the error caused by excessive electrode resistance considerably, but would not eliminate it completely. It would also afford no means of recognizing artifacts caused in this way or due to disconnection of an electrode during registration of the tracing.

3. The standardizing circuit could be placed at the entrance of the electrocardiograph instead of between the central terminal and the amplifiers. A 1.0 mv potential can, for instance, be inserted in turn into each of the limb lead and chest lead cables. This would require more time for standardization, but the standardization potential would then be affected in the same way as the

electrocardiogram by varying electrode resistance, and the true potential could always be determined by comparison with the standardization potential. If an electrode becomes disconnected, no standardization will appear in the two leads containing this electrode.

4. An alternate method would be to provide a separate terminal for unipolar and augmented unipolar leads for each amplifier channel. This would necessitate the use of four-deck instead of two-deck switches[4] but would not cause an increase of more than 1 per cent in the cost or bulk of a multiple-channel electrocardiograph. To be sure, completely correct electrocardiographic potentials in standard limb leads would be obtained even in this case only if all channels register these leads.

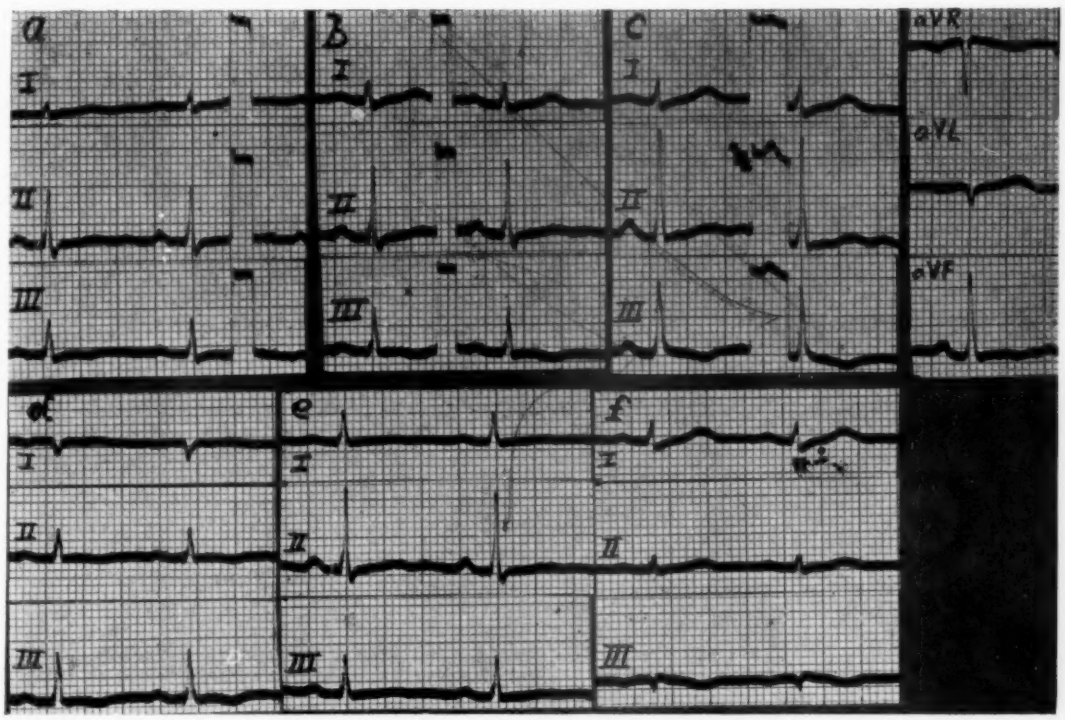

Fig. 2.—Electrocardiogram of a subject with normal heart, registered with a multiple-channel electrocardiograph with common V and aV terminals. *a*, With dry limb electrodes. *b*, With electrode paste. *c*, With electrode paste after prolonged rubbing. *d*, With right-arm electrode disconnected. *e*, With left-arm electrode disconnected. *f*, With left-leg electrode disconnected.

Multiple-channel electrocardiographs similar to the one described in this communication are now in use in hundreds of hospitals and laboratories. The instruction books supplied with each machine do not mention the peculiarities of the circuit at the entrance of the patient terminals, nor do they emphasize the possibility of occurrence of the artifacts described above. An operator accustomed to single-channel amplifier electrocardiographs may not be conscious of this possibility and may not take the measures outlined in Point 1 above, causing faulty tracing to be registered without his knowledge.

The simplest method of determining whether an electrocardiograph has the circuit described above is to see whether an electrocardiogram is still registered in one of the standard limb lead positions even after one of the limb electrodes contained in this lead has been disconnected. If this is the case, one or more of the measures outlined in the preceding paragraph should be taken. It is to be hoped that the manufacturers of electrocardiographs will take these measures into consideration in their future models.

SUMMARY

In multichannel electrocardiographs using the same V and aV terminals for all channels, increase of electrode resistance may cause gross distortion of the amplitude or configuration of the electrocardiogram in standard limb leads, without the operator being aware of this. The nature and cause of this distortion is described, and several suggestions are made to minimize it or eliminate it completely.

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A MATHEMATICAL METHOD TO DETERMINE ELECTRICAL AXIS DIRECTION OF ELECTROCARDIOGRAPHIC WAVES

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ACCEPTING the validity of Einthoven's triangle and the exactitude of Wilson's leads, it is possible to determine the electrical axis direction of P ($\tilde{A}_P$), QRS ($\tilde{A}_{QRS}$), T ($\tilde{A}_T$) and QRST ($\tilde{A}_{QRST}$), with the help of the following formulas:

1. $\text{Tan } X = \dfrac{1.1548\ DII}{DI} - 0.5774$

2. $\text{Tan } X = \dfrac{1.1548\ DIII}{DI} + 0.5774$

3. $\text{Cot } (X\text{-}30) = \dfrac{1.1548\ DII}{DIII} - 0.5774$

4. $\text{Tan } (X+30) = \dfrac{1.1548\ V_F}{V_L} + 0.5774$

5. $\text{Tan } (X\text{-}30) = \dfrac{1.1548\ V_R}{V_L} + 0.5774$

6. $\text{Cot } X = -\dfrac{1.1548\ V_R}{V_F} - 0.5774$

Substituting in the above formulas those letters which abridge the limb leads by the algebraic sum of positive and negative areas of the wave in study, we will obtain the correspondent tangent to the angle that the vector forms with with the horizontal axis (0 degree, 180 degrees) angle which indicates the vector direction.

We must keep in mind the fact that if the vector is situated to the left of the vertical axis (+90 degrees, −90 degrees), the result of the employed formula must be subtracted to 180 degrees, being the subtract result, the angle sought; " . . . trigonometric functions of the same name of two supplementary angles are equals and with contrary signs, except the sinus and cosecant which have the same sign."

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TABLES OBTAINED BY MEANS OF APPLICATION OF FORMULAS (*see page 75*)

The results of the application of each formula on 400 theoretical cases are found in the following tables.

They give, for the same electrocardiogram, the same result, whenever the condition $V_R + V_L + V_F = 0$ is true.

They permit, if this condition is not realized, the electrical axis direction to be obtained by means of the average of the results found in all the tables.

The approximation of the result is from 0° 0′ to 0° 30′, an unfortunate factor of error; if we want to correct that error, we can use the corresponding formula.

If the algebraic sum of the positive and negative areas of the waves or complexes in study does not correspond to an entire number, the superior and inferior ciphers shall be shared.

If the result of this same algebraic sum is greater than +10 or lesser than −10, we will divide both factors by a convenient number, but always both by the same number.

We can use the tables of standard limb leads, obtaining these from the unipolar limb leads, with the help of the formulas:

$$DI = V_L - V_R$$

$$DII = V_F - V_R$$

$$DIII = V_F - V_L$$

In the same way, we can use the tables of the unipolar limb leads, obtaining these from the standard leads:

$$V_R = \frac{DI + DIII}{3}$$

$$V_L = \frac{DI - DIII}{3}$$

$$V_F = \frac{DII + DIII}{3}$$

TABLE I*

DII \ DI	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	150	145	139	133	127	120	113	107	101	95	85	81	77	74	71	68	66	64	62	60
−9	155	150	144	138	131	124	116	109	102	96	85	80	76	73	69	67	64	62	60	58
−8	161	156	150	143	136	128	120	112	104	97	84	79	75	71	68	65	62	60	58	56
−7	167	162	157	150	142	134	125	115	106	98	83	78	73	69	65	63	60	58	56	54
−6	173	169	164	158	150	141	131	120	109	99	82	76	71	67	63	60	57	55	53	52
−5	180	177	172	166	159	150	139	127	113	101	81	74	68	64	60	57	54	52	51	49
−4	173	177	180	175	169	161	150	136	120	104	79	71	65	60	56	53	51	49	47	46
−3	167	169	172	175	180	173	164	150	131	109	76	67	60	55	52	49	47	45	44	43
−2	161	162	164	166	169	173	180	169	150	120	71	60	53	49	46	44	42	41	40	39
−1	155	156	157	158	159	161	164	169	180	150	60	49	44	41	39	38	37	36	35	35
+1	145	145	144	143	142	141	139	136	131	120	30	0	11	16	19	21	22	23	24	25
+2	141	140	139	138	136	134	131	127	120	109	60	30	11	0	7	11	14	16	18	19
+3	137	136	135	133	131	128	125	120	113	104	71	49	30	16	7	0	5	8	11	13
+4	134	133	131	129	127	124	120	115	109	101	76	60	44	30	19	11	5	0	4	7
+5	131	129	128	126	123	120	116	112	106	99	79	67	53	41	30	21	14	8	4	0
+6	128	127	125	123	120	117	113	109	104	98	81	71	60	49	39	30	22	16	11	7
+7	126	124	122	120	117	115	111	107	102	97	82	74	65	55	46	38	30	23	18	13
+8	124	122	120	118	115	112	109	105	101	96	83	76	68	60	52	44	37	30	24	19
+9	122	120	118	116	113	111	107	104	100	95	84	78	71	64	56	49	42	36	30	25
+10	120	118	116	114	112	109	106	103	99	95	85	79	73	67	60	53	47	41	35	30

*The top line and the left column contain the respective values for each lead, from +10 to −10. These numbers indicate the algebraic sum, result of positive and negative areas in the respective lead. The electrical axis directions are expressed by degrees which vector forms with the horizontal axis. The angles are positive below the underlined numbers and are negative above (and including) the underlined numbers. (0 and 180 are ±.)

TABLE II*

DIII	DI																		
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	120	118	116	114	112	109	106	103	99	95	85	79	73	67	60	53	47	41	35	30
−9	122	120	118	116	113	111	107	104	100	95	84	78	71	64	56	49	42	36	30	25
−8	124	122	120	118	115	112	109	105	101	96	83	76	68	60	52	44	37	30	24	19
−7	126	124	122	120	117	115	111	107	102	97	82	74	65	55	46	38	30	23	18	13
−6	128	127	125	123	120	117	113	109	104	98	81	71	60	49	39	30	22	16	11	7
−5	131	129	128	126	123	120	116	112	106	99	79	67	53	41	30	21	14	8	4	0
−4	134	133	131	129	127	124	120	115	109	101	76	60	44	30	19	11	5	0	4	7
−3	137	136	135	133	131	128	125	120	113	104	71	49	30	16	7	0	5	8	11	13
−2	141	140	139	138	136	134	131	127	120	109	60	30	11	0	7	11	14	16	18	19
−1	145	145	144	143	142	141	139	136	131	120	30	0	11	16	19	21	22	23	24	25
+1	155	156	157	158	159	161	164	169	180	150	60	49	44	41	39	38	37	36	35	35
+2	161	162	164	166	169	173	180	169	150	120	71	60	53	49	46	44	42	41	40	39
+3	167	169	172	175	180	173	164	150	131	109	76	67	60	55	52	49	47	45	44	43
+4	173	177	180	175	169	161	150	136	120	104	79	71	65	60	56	53	51	49	47	46
+5	180	177	172	166	159	150	139	127	113	101	81	74	68	64	60	57	54	52	51	49
+6	173	169	164	158	150	141	131	120	109	99	82	76	71	67	63	60	57	55	53	52
+7	167	162	157	150	142	134	125	115	106	98	83	78	73	69	65	63	60	58	56	54
+8	161	156	150	143	136	128	120	112	104	97	84	79	75	71	68	65	62	60	58	56
+9	155	150	144	138	131	124	116	109	102	96	85	80	76	73	69	67	64	62	60	58
+10	150	145	139	133	127	120	113	107	101	95	85	81	77	74	71	68	66	64	62	60

*Same indications as in Table I. The values in the top line correspond to DI, and those of the left column correspond to DIII.

TABLE III*

DII	DIII																			
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	90	95	101	107	113	120	127	133	139	145	155	159	163	166	169	172	174	176	178	180
−9	85	90	96	102	109	116	124	131	138	144	155	160	164	167	171	173	176	178	180	178
−8	79	84	90	97	104	112	120	128	136	143	156	161	165	169	172	175	178	180	178	176
−7	73	78	83	90	98	106	115	125	134	142	157	162	167	171	175	178	180	178	176	174
−6	67	71	76	82	90	99	109	120	131	141	158	164	169	173	177	180	177	175	173	172
−5	60	64	68	74	81	90	101	113	127	139	159	166	172	176	180	177	174	172	171	169
−4	53	56	60	65	71	79	90	104	120	136	161	169	175	180	176	173	171	169	167	166
−3	47	49	52	55	60	67	76	90	109	131	164	173	180	175	172	169	167	165	164	163
−2	41	42	44	46	49	53	60	71	90	120	169	180	173	169	166	164	162	161	160	159
−1	35	36	37	38	39	41	44	49	60	90	180	169	164	161	159	158	157	156	155	155
+1	25	25	24	23	22	21	19	16	11	0	90	120	131	136	139	141	142	143	144	145
+2	21	20	19	18	16	14	11	7	0	11	60	90	109	120	127	131	134	136	138	139
+3	17	16	15	13	11	8	5	0	7	16	49	71	90	104	113	120	125	128	131	133
+4	14	13	11	9	7	4	0	5	11	19	44	60	76	90	101	109	115	120	124	127
+5	11	9	8	6	3	0	4	8	14	21	41	53	67	79	90	99	106	112	116	120
+6	8	7	5	3	0	3	7	11	16	22	39	49	60	71	81	90	98	104	109	113
+7	6	4	2	0	3	5	9	13	18	23	38	46	55	65	74	82	90	97	102	107
+8	4	2	0	2	5	8	11	15	19	24	37	44	52	60	68	76	83	90	96	101
+9	2	0	2	4	7	9	13	16	20	25	36	42	49	56	64	71	78	84	90	95
+10	0	2	4	6	8	11	14	17	21	25	35	41	47	53	60	67	73	79	85	90

*Same indications as in Tables I and II.

TABLE IV*

V_F	V_L																		
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	150	148	146	144	142	139	136	133	129	125	115	109	103	97	90	83	77	71	66	60
−9	151	150	148	145	143	141	137	134	130	126	114	108	101	94	86	79	72	66	60	54
−8	154	152	150	147	145	142	139	135	131	126	113	106	98	90	82	74	67	60	54	49
−7	156	155	152	150	147	145	141	137	132	127	112	104	95	85	76	68	60	53	48	43
−6	158	157	154	152	150	147	143	139	134	128	111	101	90	79	69	60	52	46	41	37
−5	161	159	158	155	153	150	146	142	136	129	109	97	83	71	60	51	44	38	34	30
−4	164	162	161	159	157	154	150	145	139	131	106	90	74	60	49	41	35	30	26	23
−3	167	166	165	163	161	158	154	150	143	134	101	79	60	46	37	30	26	22	19	17
−2	170	170	169	168	166	164	161	157	150	139	90	60	41	30	23	19	16	14	12	11
−1	175	175	174	173	172	171	169	166	161	150	60	30	19	14	11	9	8	7	6	5
+1	175	174	173	172	171	169	166	161	150	120	30	19	14	11	9	8	7	6	5	5
+2	169	168	166	164	161	157	150	139	120	90	41	30	23	19	16	14	12	11	10	10
+3	163	161	158	154	150	143	134	120	101	79	46	37	30	26	22	19	17	15	14	13
+4	157	154	150	145	139	131	120	106	90	74	49	41	35	30	26	23	21	19	18	16
+5	150	146	142	136	129	120	109	97	83	71	51	44	38	34	30	27	25	22	21	19
+6	143	139	134	128	120	111	101	90	79	69	52	46	41	37	33	30	28	26	23	22
+7	137	132	127	120	112	104	95	85	76	68	53	48	43	39	35	33	30	28	25	24
+8	131	126	120	113	106	98	90	82	74	67	54	49	45	41	38	35	33	30	28	26
+9	126	120	114	108	101	94	86	79	72	66	54	50	46	43	39	37	35	32	30	29
+10	120	114	109	103	97	90	83	77	71	65	55	51	47	44	41	38	36	34	32	30

*Table obtained with V_L (in the top line), and V_F (in the left column). The angles are positive when V_F is positive too, and vice versa.

TABLE V*

V_R	V_L																		
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	90	88	86	84	82	79	76	73	69	65	54	49	43	37	30	23	17	11	5	0
−9	92	90	88	86	83	81	77	74	70	65	54	48	41	34	26	19	12	6	0	5
−8	94	92	90	88	85	82	79	75	71	66	53	46	38	30	22	14	7	0	6	11
−7	96	94	92	90	87	84	81	77	72	67	52	44	35	26	16	8	0	7	12	17
−6	98	97	95	93	90	87	83	79	74	68	51	41	30	19	9	0	8	14	19	23
−5	101	99	98	95	93	90	86	82	76	69	49	37	23	11	0	9	16	22	26	30
−4	104	103	101	99	97	94	90	85	79	71	46	30	14	0	11	19	26	30	34	37
−3	107	106	105	103	101	98	95	90	83	74	41	19	0	14	23	30	35	38	41	43
−2	111	110	109	108	106	104	101	97	90	79	30	0	19	30	37	41	44	46	48	49
−1	115	115	114	113	112	111	109	106	101	90	0	30	41	46	49	51	52	53	54	55
+1	125	126	127	128	129	131	134	139	150	180	90	79	74	71	69	68	67	66	65	65
+2	131	132	134	136	139	143	150	161	180	150	101	90	83	79	76	74	72	71	70	69
+3	137	139	142	145	150	157	166	180	161	139	106	97	90	85	82	79	77	75	74	73
+4	143	146	150	154	161	169	180	166	150	134	109	101	95	90	86	83	81	79	77	76
+5	150	154	158	164	171	180	169	157	143	131	111	104	98	94	90	87	84	82	81	79
+6	157	161	166	172	180	171	161	150	139	129	112	106	101	97	93	90	87	85	83	82
+7	163	168	173	180	172	164	154	145	136	128	113	108	103	99	95	93	90	88	86	84
+8	169	174	180	173	166	158	150	142	134	127	114	109	105	101	98	95	92	90	88	86
+9	175	180	174	168	161	154	146	139	132	126	115	110	106	103	99	97	94	92	90	88
+10	180	175	169	163	157	150	143	137	131	126	115	111	107	104	101	98	96	94	92	90

*Table obtained with V_L (in the top line) and with V_R (in the left column). The angles are positive above (and including) the underlined numbers and they are negative below underlined numbers.

TABLE VI*

V_R	V_F																			
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
−10	30	29	26	24	22	19	16	13	10	5	5	11	17	23	30	37	43	49	54	60
−9	32	30	28	25	23	21	18	14	10	5	6	12	19	26	34	41	48	54	60	66
−8	34	32	30	28	26	22	19	15	11	6	7	14	22	30	38	46	53	60	66	71
−7	36	35	33	30	28	25	21	17	12	7	8	16	26	35	44	52	60	67	72	77
−6	38	37	35	33	30	27	23	19	14	8	9	19	30	41	51	60	68	74	79	83
−5	41	39	38	35	33	30	26	22	16	9	11	23	37	49	60	69	76	82	86	90
−4	44	43	41	39	37	34	30	26	19	11	14	30	46	60	71	79	85	90	94	97
−3	47	46	45	43	41	38	35	30	23	14	19	41	60	74	83	90	95	98	101	103
−2	51	50	49	48	46	44	41	37	30	19	30	60	79	90	97	101	104	106	108	109
−1	55	54	54	53	52	51	49	46	41	30	60	90	101	106	109	111	112	113	114	115
+1	65	66	67	68	69	71	74	79	90	120	150	139	134	131	129	128	127	126	126	125
+2	71	72	74	76	79	83	90	101	120	150	161	150	143	139	136	134	132	131	130	129
+3	77	79	82	85	90	97	106	120	139	161	166	157	150	145	142	139	137	135	134	133
+4	83	86	90	95	101	109	120	134	150	166	169	161	154	150	146	143	141	139	137	136
+5	90	94	98	104	111	120	131	143	157	169	171	164	158	154	150	147	145	142	141	139
+6	97	101	106	112	120	129	139	150	161	171	172	166	161	157	153	150	147	145	143	142
+7	103	108	113	120	128	136	145	154	164	172	173	168	163	159	155	152	150	147	145	144
+8	109	114	120	127	134	142	150	158	166	173	174	169	165	161	158	154	152	150	148	146
+9	115	120	126	132	139	146	154	161	168	174	175	170	166	162	159	157	155	152	150	148
+10	120	126	131	137	143	150	157	163	169	175	175	170	167	164	161	158	156	154	151	150

*Table obtained with V_F (in the top line), and V_R (in the left column). The angles are positive when V_F is positive too, and vice versa.

The cases in which the algebraic sum of the positive and negative areas results in zero were omitted, because then we know the result beforehand. This is true for all the tables.

DEMONSTRATION OF THE PROPOSED FORMULAS

Formula 1.—$\tan X = \dfrac{1.1548\ DII}{DI} - 0.5774$ (See Fig. 1.)

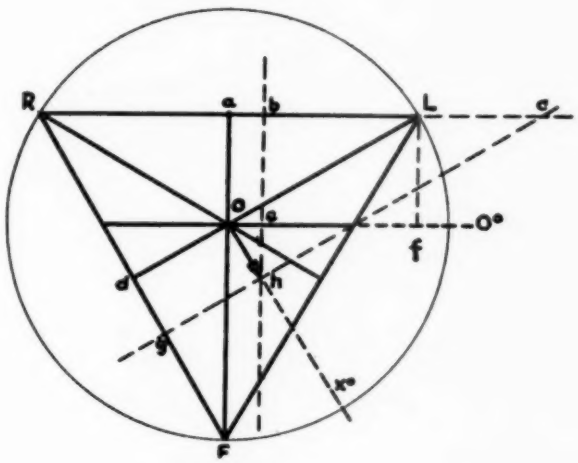

FIG. 1

1. $\tan X = \dfrac{eh}{Oe}$; $Oe = ab = DI$

   $\therefore \tan X = \dfrac{eh}{DI}$

2. $eh = bh - be$
   $bh = bc.\ \tan 30 = 0.5774\ bc$
   $be = Lf = OL.\ \sin 30 = 0.5$
   (OL is radius of circle = 1)
   $\therefore eh = 0.5774\ bc - 0.5$

3. $bc = Rc - Rb$

   $Rc = \dfrac{Rg}{\cos 60} = 2\ Rg$

   $Rb = Ra + ab$
   $\therefore bc = 2\ Rg - (Ra + ab)$

4. $Rg = Rd + dg$
   $Rd = OR.\ \cos 30 = 0.8661$ (OR is radius of circle);
   $dg = DII$ $\therefore Rg = 0.8661 + DII$

5. $Ra = Rd = 0.8661$; $ab = DI$

6. $bc = 2\ Rg - (Ra + ab) = 2\ Rg - Ra - ab$
   $\therefore bc = 2(0.8661 + DII) - 0.8661 - DI = 0.8661 + 2\ DII - DI$

7. $eh = 0.5774\ bc - 0.5$;
   $\therefore eh = 0.5774\ (0.8661 + 2\ DII - DI) - 0.5 =$
   $0.5 + 1.1548\ DII - 0.5774\ DI - 0.5 = 1.1548\ DII - 0.5774\ DI$

8. Therefore:

$$\tan X = \frac{1.1548\ DII - 0.5774\ DI}{DI}$$

$$\therefore \tan X = \frac{1.1548\ DII}{DI} - 0.5774$$

Formula 2.—$\tan X = \frac{1.1548\ DIII}{DI} + 0.5774$ (See Fig. 2.)

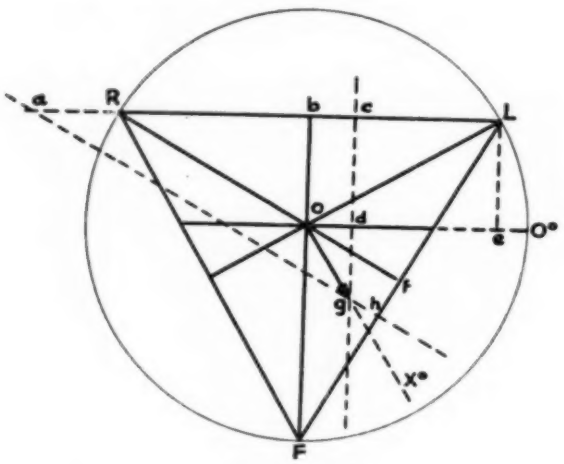

FIG. 2

1. $\tan X = \frac{dg}{Od}$; $Od = DI$

$$\therefore \tan X = \frac{dg}{DI}$$

2. $dg = cg - cd$
   $cg = ac.\ \tan 30 = 0.5774\ ac$
   $cd = Le = OL.\ \sin 30 = 0.5$
   (OL is radius of circle)
   $\therefore dg = 0.5774\ ac - 0.5$
3. $ac = aL - cL$

$$aL = \frac{Lh}{\cos 60} = 2\ Lh$$

   $cL = bL - bc$
   $\therefore ac = 2\ Lh - (bL - bc)$
4. $Lh = Lf + fh$;
   $Lf = OL.\ \cos 30 = 0.8661$; $fh = DIII$
   $\therefore Lh = 0.8661 + DIII$
5. $bL = Lf = 0.8661$; $bc = DI$
6. $ac = 2Lh - (bL - bc) = 2\ Lh - bL + bc$
   $\therefore ac = 2(0.8661 + DIII) - 0.8661 + DI = 0.8661 + 2\ DIII + DI$

7. $dg = 0.5774\ ac - 0.5$
   $\therefore dg = 0.5774\ (0.8661 + 2\ DIII + DI) - 0.5 =$
   $0.5 + 1.1548\ DIII + 0.5774\ DI - 0.5 = 1.1548\ DIII + 0.5774\ DI$
8. Therefore:

$$\tan X = \frac{1.1548\ DIII + 0.5774\ DI}{DI}$$

$$\therefore \tan X = \frac{1.1548\ DIII}{DI} + 0.5774$$

Formula 3.—$\cot (X-30) = \dfrac{1.1548\ DII}{DIII} - 0.5774$ (See Fig. 3.)

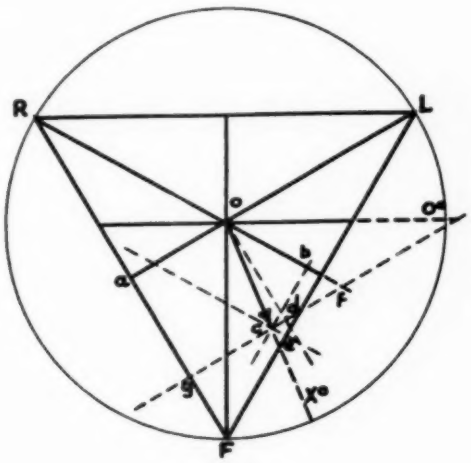

FIG. 3

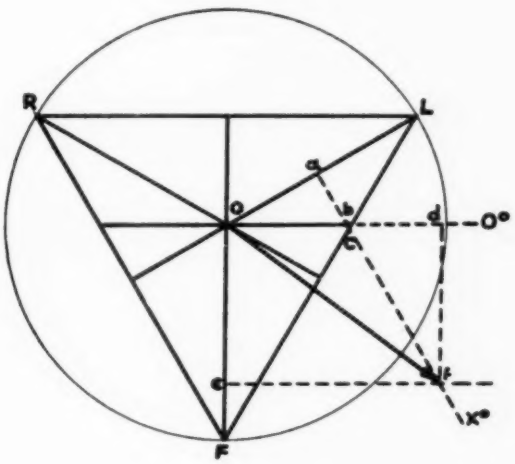

FIG. 4

1. $\cot (X-30) = \dfrac{Ob}{bc}$; $bc = DIII$

$$\therefore \cot (X-30) = \frac{Ob}{DIII}$$

2. $Ob = Of - bf$

$$Of = \frac{Od}{\cos 30} = \frac{DII}{0.8661} = 1.1548\ DII$$

$bf = bc.\ \tan 30 = 0.5774\ DIII$
$\therefore Ob = 1.1548\ DII - 0.5774\ DIII$

3. Therefore:

$$\cot (X-30) = \frac{1.1548\ DII - 0.5774\ DIII}{DIII}$$

$$\therefore \cot (X-30) = \frac{1.1548\ DII}{DIII} - 0.5774$$

Formula 4.—$\tan (X+30) = \dfrac{1.1548\ V_F}{V_L} + \dfrac{0.5774}{af}$ (See Fig. 4.)

1. $\tan (X+30) = \dfrac{af}{Oa}$; $Oa = V_L$

$\therefore \tan (X+30) = \dfrac{af}{V_L}$

2. $af = ab + bf$

$ab = V_L \tan 30 = 0.5774\ V_L$

$bf = \dfrac{fd}{\cos 30} = \dfrac{V_F}{0.8661} = 1.1548\ V_F$

$\therefore af = 1.1548\ V_F + 0.5774\ V_L$

3. Therefore:

$\tan (X+30) = \dfrac{1.1548\ V_F + 0.5774\ V_L}{V_L}$

$\therefore \tan (X+30) = \dfrac{1.1548\ V_F}{V_L} + 0.5774$

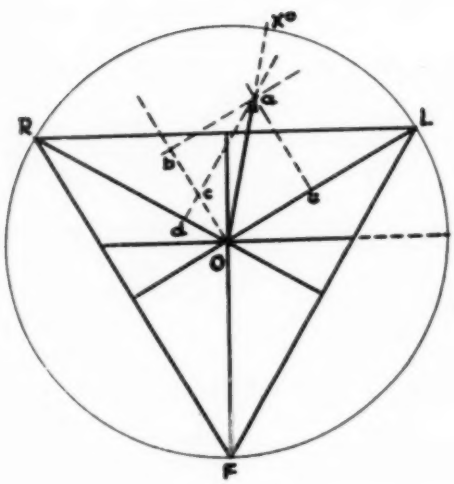

FIG. 5

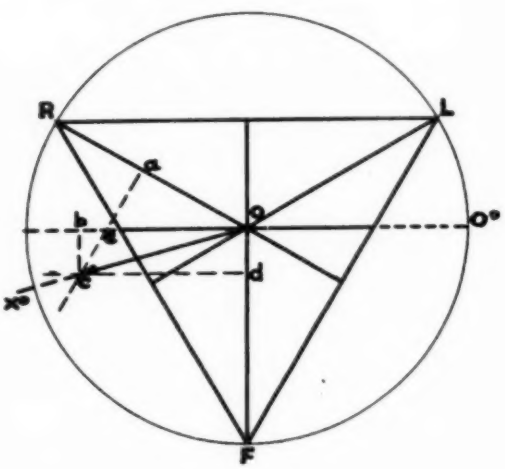

FIG. 6

Formula 5.—$\tan (X-30) = \dfrac{1.1548\ V_R}{V_L} + 0.5774$ (See Fig. 5.)

1. $\tan (X-30) = \dfrac{ae}{Oe}$; $Oe = V_L$

$\therefore \tan (X-30) = \dfrac{ae}{V_L}$

2. $ae = Ob = Oc + cb$

$$Oc = \frac{Od}{\cos 30} = \frac{V_R}{0.8661} = 1.1548\ V_R$$

$$cb = ab.\ \tan 30 = 0.5774\ V_L$$

$$\therefore\ ae = 1.1548\ V_R + 0.5774\ V_L$$

3. Therefore:

$$\tan (X-30) = \frac{1.1548\ V_R + 0.5774\ V_L}{V_L}$$

$$\therefore\ \tan (X-30) = \frac{1.1548\ V_R}{V_L} + 0.5774$$

Formula 6.—$$\text{Cot } X = -\frac{1.1548\ V_R}{V_F} - 0.5774$$ (See Fig. 6.)

1. $$\cot (180-X) = \frac{Ob}{bc};\quad bc = Od = V_F$$

$$\therefore\ \cot (180-X) = \frac{Ob}{V_F}$$

2. $Ob = Oe + eb$

$$Oe = \frac{Oa}{\cos 30} = \frac{V_R}{0.8661} = 1.1548\ V_R$$

$$eb = bc.\ \tan 30 = 0.5774\ V_F$$

$$\therefore\ Ob = 1.1548\ V_R + 0.5774\ V_F$$

3. Therefore:

$$\cot (180-X) = \frac{1.1548\ V_R + 0.5774\ V_F}{V_F}$$

$$\cot (180-X) = -\cot X$$

$$\therefore\ \cot X = -\frac{1.1548\ V_R}{V_F} - 0.5774$$

SUMMARY AND CONCLUSIONS

An exact method to determine the electrical axis direction is presented, with the help of precise mathematical formulas.

By means of the theoretical application of the formulas a series of tables which have 400 cases were obtained, with values for each lead from +10 to −10.

The practical application of the formulas gives the greatest possible exactitude, but the tables have more utility, because they reunite rapidity and approximation of almost insignificant degree fractions.

The proposed procedure is applicable to all electrocardiographic waves or complexes, such as, P ($\bar{A}_P$), QRS ($\bar{A}_{QRS}$), T ($\bar{A}_T$) and QRST ($\bar{A}_{QRST}$) or ventricular gradient).

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THE MEASUREMENT OF THE DURATION OF THE QRS INTERVAL

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AN EXACT measurement of the duration of the QRS interval is of great importance in the diagnosis of complete or incomplete bundle branch block and of other intraventricular conduction disturbances. It is also important whenever the effect of different drugs and procedures on the rate of intraventricular conduction is to be studied in detail. The determination of the QRS duration in routine electrocardiography is usually considered so easy and certain that no mention is made of the exact method of measurement whenever the QRS duration is discussed. However, if exact and objective measurements must be carried out, many sources of possible error become apparent, so that the values of QRS obtained by different electrocardiographers may vary as much as 0.05 second. These sources of error may be subdivided into three groups: differences in the duration of QRS of each heart beat in different leads, differences in the duration of successive QRS complexes, and difficulties in the determination of the points indicating the beginning and the end of the QRS complex. The purpose of the present paper is to discuss these sources of error and to attempt to set up concrete and objective rules for the measurement of the QRS interval.

1. *Differences in the Apparent QRS Duration in Different Leads.*—The QRS interval must be defined as beginning at the instant when ventricular activation (depolarization) causes the first measurable deflection of the electrocardiographic tracing, and ending at the instant when the last measurable deflection caused by this activation is terminated. If an electrocardiographic lead is perpendicular to the initial or terminal electric vectors appearing during ventricular activation, the initial or terminal parts of QRS will be isoelectric in this lead and the QRS duration as measured in this lead will appear shorter than in other leads.

In the standard limb leads, the initial or terminal part of QRS may be isoelectric in Lead I if the projection of the corresponding vectors on the frontal plane has a value of ±90 degrees; it is isoelectric in Lead II if the direction of this projection is −30 degrees or +150 degrees, and in Lead III if this direction is +30 degrees or −150 degrees. In the unipolar limb leads, these values are −60 degrees and +120 degrees for aV_R, +60 degrees and −120 degrees for aV_L, and 0 degree and 180 degrees for aV_F. It was early recognized that the QRS

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complex may begin as much as 0.02 second earlier or end a similar length of time later in some of the limb leads than in others.[4,12] It has therefore become the custom to take the longest QRS duration in any of the limb leads as the true QRS duration.[1,3,5,9,12,16] However, QRS does not necessarily begin earliest and end latest in the same lead; in fact, this is very rarely the case. In Fig. 1, for instance, QRS begins earliest in Leads II and III, but ends latest in Lead I. Accordingly, the true QRS duration in the limb leads can be determined only if at least two of these leads are taken synchronously.

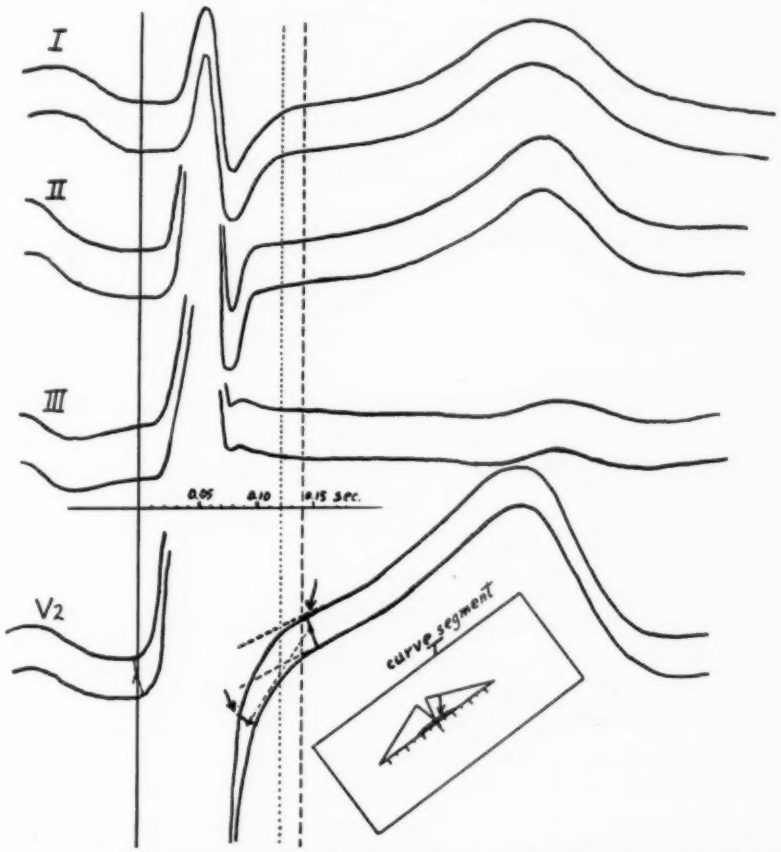

Fig. 1.—Leads I, II, III, and V_2 of a normal person, registered synchronously. The electrocardiograms were enlarged about ten times and the upper and lower edges of the curve retraced accurately. The solid vertical line shows the time of the earliest measurable point of QRS. The dotted line denotes the time of the latest point on QRS, measured according to the method of the mid-point of the RS-T junction. The interrupted line shows this time, as measured according to the method of the least slope of RS-T. Below Lead V_2, the instrument for measuring the curvature of the RS-T junction is represented. The arrows indicate the beginning and end of the RS-T junction in Lead V_2.

If only a single-channel electrocardiograph is available, the three standard or unipolar limb leads, taken separately at the same sensitivity, can be synchronized after registration. This is accomplished in the following manner[8]: The tracings of the three Leads I, II, and III or aV_R, aV_L, and aV_F are placed side by side parallel to each other, covered by a ruler placed parallel to the time lines, and moved horizontally until the value of the deflection at their point of intersection with the edge of the ruler in Lead II is equal to the sum of these values in Leads I and III,

or until the sums of these values in Leads aV_R, aV_L, and aV_F are equal to zero. If no such position can be found with a given set of complexes, these complexes were evidently registered during different phases of respiration, at different heart positions; in this case the procedure must be repeated using another set of complexes. As soon as the correct time relation of the set of complexes is established in this way, the interval from the earliest point of QRS in any one of the leads to the latest point in any lead is taken as the correct QRS duration.

In precordial leads, the QRS duration was found longer than in limb leads.[1,8,10] In precordial leads the QRS complex usually begins earlier than in limb leads,[8] as the voltage of the former is higher and the initial vector of QRS usually has an anterior direction, corresponding to the activation of the ventricular septum from left to right. In our material, the beginning of QRS occurred up to 0.02 second earlier in Lead V_2 than in the limb leads. In Fig. 1 this difference is 0.018 second. However, this applies primarily to the Leads V_{1-2} and V_{5-6}, while the intermediate leads facing the septum may show an isoelectric beginning of QRS, since the septal activation takes place perpendicular to the direction of these leads. In cases which showed a sharp RS-T junction (Section 3) in the chest leads, this usually occurred approximately at the same time as in the limb leads. In cases where the RS-T junction was gradual, the end of QRS usually appeared to occur later than in the limb leads, the difference varying according to the method of measurement. (See Section 3.)

In all of the larger statistical studies concerning the normal limits of the QRS duration, nonsynchronized leads were used.[8] As mentioned in the preceding paragraphs, measurement of the QRS duration from the earliest to the latest point of a large number of synchronized limb and chest leads gives values up to 0.03 second higher than those obtained by measuring nonsynchronized limb leads. These higher values must be necessarily considered to approach the true QRS duration better than those obtained by conventional measurements. The increasing use of multichannel electrocardiographs and of vectorcardiographs makes it possible to measure conveniently the duration of the QRS complex from the first to the last vectors responsible for it, and it is to be assumed that this method will be used more and more widely as time goes on. In order to make proper evaluation of the QRS duration measured in this way possible, it would be necessary to establish completely new limits for this duration on a large series of normal persons. In our limited series of cases the upper normal limit of QRS was, for instance, about 0.013 second, which would be considered definitely a pathologic value if judged by the criteria now in use.

2. *Differences in the QRS Duration in Successive Heart Beats.*—The variability in the duration of QRS in successive complexes of the same lead was found to be about 0.003 second.[7] These variations were attributed to respiratory changes of the heart position, and therefore to differences in the projection of the QRS vector loop on a certain lead. If the beginning and end of QRS is measured in at least three synchronized leads not lying in the same plane, the terminal and initial QRS vectors would be registered at least in some of these leads regardless of the heart position, and the positional variability would be negligible. The variability in the duration of synchronized QRS complexes can be caused by physiologic factors such as changes in the speed of ventricular con-

duction due to phasic variations in the vagal and symphathetic tone and in the diastolic ventricular volume during respiration. An even more important factor is the variability of measurement[8] (see Section 3), which accounted for nearly the entire variability found in the same persons on different days.[14] In order to further reduce the error due to this variability, it is recommended to make measurements on at least three to five successive synchronized QRS complexes, or all the complexes of a respiratory cycle and to average these values.

3. *Determination of the Beginning and End of QRS.*—Whenever an exact determination of certain points on the electrocardiographic curve is to be made, it is necessary to consider the limitations and sources of error which appear when variations of electric potential are transformed into a graphic curve. The electrocardiographic tracing has not only a vertical, but also a horizontal thickness; this is determined by the width of the point of contact which the recording instrument makes with the electrocardiographic paper. This width is smallest in the case of optically recording instruments, where it is in the order of one millisecond at the conventional paper speed. It is appreciably greater in the thermic direct-writing instruments, where the point of contact between the sylus and the paper, plus the area where radiation from the stylus is intense enough to turn the paper black, may be as much as 0.01 second. The width is about the same in the ink-writing instruments. In the case of an upward excursion of the trace, the upper edge of the curve will apparently leave the base line up to 0.01 second earlier and will return to it correspondingly later than the lower edge of the tracing. In order to obtain correct values, measurements must be therefore made of the upper as well as the lower edges of the tracing, and an average taken of these readings. The differences will be the same in millimeters if the paper speed is increased, but will correspond to a smaller period of time between the time lines. The errors will be therefore smaller if the 50 mm./sec. instead of the conventional 25 mm./sec. speed is used.

As the segment of the electrocardiographic curve immediately preceding the QRS group (the P-R segment) has almost always a much more gradual slope than that of the initial section of QRS, there is usually no difficulty in the determination of the point where the QRS complex begins in a given lead. The reason for the even slope of the P-R segment is that any electric activity appearing during it can be caused only by auricular repolarization, which causes only small potential variations as compared to those due to ventricular activation in leads from the body surface. The end of the QRS complex is more difficult to determine, as the rate of the potential variations caused by ventricular repolarization more nearly approaches that of the terminal part of the QRS complex. According to the last report of the Committee on the Standardization of Electrocardiographic Nomenclature of the American Heart Association,[2] the RS-T junction is defined as the " . . . point or shoulder which marks the end of the QRS complex, the point where the steep slopes of the QRS deflection are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave." Pardee states that " . . . in most electrocardiograms that S-T junction is effected by a definite change in the inclination of the curve toward the isoelectrical level, . . . forming a more or less sharp angle at

this point. Gradual change in the inclination may occur, so that R or S curve gently into the beginning of T, sometimes taking 0.04 second or more to complete the transition."[12] Such a gradual transition between QRS and RS-T is especially common in the precordial Leads V_1 to V_4, where the slope of the ascending RS-T segment approaches that of the terminal section of the S wave. It is evident that subjective selection of one point in such a gradual transition to represent the end of QRS would result in a great variability of the QRS duration as measured by different observers or even by the same observer at different times.

In many of the published cases, a wide RS-T junction was an artifact due to an insufficiently short deflection time of the electrocardiograph which in some cases exceeded 0.04 second. This occurred either when the string tension in a string galvanometer had to be decreased as a consequence of high skin resistance, or when a condenser was purposely introduced parallel to the patient in order to suppress A. C. interference and muscle tremor.[8] In our cases, a four-channel Sanborn Poly-Viso electrocardiograph with a deflection time of 0.09 second for a square-wave response was used. The lag of response for the QRS potentials, which are considerably less steep than a square wave,[8] must have been appreciably less. Thus, any RS-T junction exceeding 0.01 second in duration could not have been due to an insufficiently fast response of the electrocardiograph.

In order to avoid the subjective errors of determining the end of QRS in the presence of a gradual transition between QRS and RS-T, German authors who attempted to draw clinical conclusions from the changes in the duration of QRS after exercise[6,15] proposed to measure a part of QRS instead of the whole. They measured the distance between the beginning of QRS and the apex of the S wave, a notch in the terminal part of QRS, or the transition between a rapidly descending or ascending terminal limb of QRS, where the curve is thin, into a slow terminal section of this limb, where the curve is thick. It was assumed that the duration of this part of the QRS complex would vary in proportion to that of the entire complex. However, it was pointed out that in the latter case the transition is too gradual to be determined accurately, and that in all cases the relation of the easily measurable points of the QRS complex to the duration of the entire complex shows great variability in different persons as well as in the same person under different conditions.[11,13] The method of measuring the duration of only a part of QRS and making conclusions as to the duration of the entire QRS complex from these values must accordingly be rejected. In order to put the determination of the end of a gradual RS-T junction on a more objective basis, several methods were tried; these will be described in the following paragraphs.

As mentioned at the beginning of this section, a sudden decrease of slope seems to be the criterion most widely used in the subjective determination of the end of QRS. This is theoretically justified, as in the single cardiac muscle fiber the process of depolarization is at least 100 times as rapid as that of repolarization,[8] while the total changes of voltage produced by the two processes are the same. To be sure, in a precordial lead the voltage changes caused by electromotive forces arising in sections of the ventricle near the precordial electrode are up to five times as great as those arising in parts of the ventricle farthest away from this electrode,[8] so that the difference in the slope of the deflections in this lead due to repolarization in the former and depolarization in the latter may not be as great as in leads from single muscle fibers, but such differences can nevertheless be expected even in the precordial leads. Accordingly, a change in

slope should always appear at the end of the QRS complex. The problem is how to determine this change objectively.

One method of determining a change in slope is to measure the actual slope of the curve in millivolts per second for every point of the curve in the smooth RS-T junction and on both sides of it. The difference in the slope of two adjacent sections of the curve, or the change in slope per unit time, can then be determined in millivolts per second.[2] This laborious procedure can be avoided, if not the actual rate of change of slope, but only the point of maximal change of slope or the relative curvature are to be determined. An exact determination of the curvature is possible only if the tracing is enlarged about ten times by means of a projector, and a photograph is made of it, or the upper and lower borders of the tracing are outlined as exactly as possible by retracing them with a sharp pencil. A triangular opening illustrated at the RS-T junction of Lead V_2 in Fig. 1 is cut out of a sheet of paper so that the distance between the tip of the pointer and the straight line at the base of the triangle equals 0.5 mm. A strip of electrocardiograph paper with well-defined lines is pasted as a scale along the edge of this base, which should be at least 3 cm. long. The opening is placed on the enlarged tracing so that the tip of the pointer just touches the outer convex edge of the curve in the region of the RS-T junction. The paper is then rotated around this point of contact until the convex edge of the curve intersects the base of the triangle at equal distances from the pointer; the value of these distances is kept in mind while the pointer is moved to the next point of the curve. In this way the entire region of the RS-T junction is explored at intervals of 1 to 2 mm. until a point or points on the curve are found which give the least distance to the points of intersection on the base of the triangle. As the location of this point shows considerable variability as a consequence of chance deviations from the true course of the curve, originating during its reproduction, it was held more exact to determine the beginning and the end of the segment with greatest curvature, which corresponds to the RS-T junction, and to take the mid-point between these two points as indicating the end of the QRS complex. These two points are difficult to define exactly, but the most practical definition appeared to be that the distance of the points of intersection just mentioned should be twice as great at the ends of the RS-T junction than at the point of this junction showing greatest curvature. In other words, the longest segment of the curve which does not deviate more than 0.5 mm. from a straight line is twice as long at the ends of the RS-T junction as at the point of its greatest curvature. This method of measurement will be designated as that of the "mid-point of the RS-T junction."

If the RS-T junction is sharp, its beginning and end as well as its mid-point can be located even with the naked eye on the original tracing. If the curvature of the RS-T junction is very gradual and approaches the arc of a circle, the detailed method outlined above should be used if maximum accuracy is desired. In this case, it is important to retrace the course of the curve as steadily and faithfully as possible. As mentioned before, the measurements must be made on the lines corresponding to the upper as well as the lower edge of the curve, and an average of the two measurements taken. In order to test the constancy of the results obtained by this method, an electrocardiographic curve showing a wide RS-T junction was redrawn and remeasured ten times. The standard error of measurement for this method was 3.6 milliseconds, so that the probability of a single measurement deviating more than 0.01 second from the mean value would be one in a thousand in this particular case.

The second method of measurement is based on the determination of the slope of the initial section of the RS-T segment. If this slope is extended toward the beginning of QRS, the earliest point which deviates from this slope would theoretically correspond to the end of QRS. As the process of repolarization begins at a slow rate immediately after depolarization is completed, displace-

ment of the RS-T segment, which is determined by differences in the rate of repolarization in different sections of the ventricle, already begins during the earliest sections of the QRS complex and increases gradually as systole progresses. Conversely, the slope of the RS-T segment should show a continual decrease as it is followed backward toward the QRS complex. If the slope begins to increase again, this can be only due to superposition of depolarization potentials on the repolarization potentials. The first point which shows a deviation from the least slope contained in the RS-T segment must accordingly be designated as the end of QRS. If there is one point of least slope in the RS-T segment, this point is the end of QRS; if there is a straight line of least slope, the end of this line nearest the beginning of the QRS is the end of QRS. This method of determination, which will be designated as that of "least slope," has the disadvantage that chance deviations from the true course of RS-T during reproduction of the curve cause especially great variations in the location of the end of QRS determined in this way. The standard error of measurement of the electrocardiographic curve used in the preceding paragraph was 8.2 milliseconds so that one measurement in a thousand could deviate more than 0.025 second from the true value. In addition to its great variability, this method also has the disadvantage that it gives very large values for the QRS duration, the highest values found in normals being about 0.14 to 0.15 second. While such values may represent the true duration of QRS, they do not correspond to those obtained by the conventional subjective methods of measurement, which are more related to the method of the mid-point of the RS-T junction. If the method of "least slope" is to be used routinely, new normal standards first would have to be established for it. From a theoretical point of view, the method of "least slope" establishes the moment of disappearance of the last potentials due to ventricular depolarization, regardless how small they are, while the method of the mid-point of the RS-T junction measures the point where these potentials become smaller than the total potentials due to repolarization.

Several other methods were tried, but proved too vague, inconvenient, or variable for practical use. Among them was the method of measuring a point on the RS-T junction, the slope of which corresponded to a fixed number of degrees or millivolts per second. This proved unreliable as it would depend on the absolute voltage of the electrocardiogram and on the heart rate. A method which would include these variables would concern the measurement of the mean slope of the RS-T segment and the terminal portion of the QRS complex, and the determination of the point on the RS-T junction where it corresponds to this slope. The practical application of this method failed because of the impossibility to define accurately the initial section of the RS-T segment and the terminal section of the QRS complex. Another method was to take the mid-point between the point of "least slope" on the RS-T segment and the point of greatest slope in the QRS complex. While the former could be easily determined, the definition of the latter proved ambiguous. Furthermore, the QRS duration determined in this way would correspond only to a variable part of the QRS complex. Another method was based on measurement of the moment when the tracing reaches the base line or a certain percentage of the total amplitude of QRS. Such measurements would vary with the amount of displacement of the RS-T segment and would be impossible to execute correctly because of the difficulty of definition of a base line at the end of QRS.

In conclusion, the only reliable method which we could develop for the accurate measurement of the QRS duration in the presence of a gradual RS-T

junction is too laborious and complicated to be applied in routine use. The method of "least slope" can be used with the naked eye, but its variability is great and it does not give values corresponding to those obtained with the subjective methods generally in use. The only types of information which would justify the labor involved in the method of the mid-point of the RS-T junction would be the determination of the QRS duration as a measure of ventricular conduction velocity in cardiac function tests as well as the measurement of the relation between the QRS and Q-T durations as a possible explanation for certain secondary changes of the T wave. Both these methods have not yet passed beyond the experimental stage. We have seen that widely diverging values of QRS can be obtained according to whether the measurements are made on limb leads only or on limb and chest leads, and whether the leads are synchronized or not. It seems highly desirable that definite criteria for the measurement of the QRS duration should be established.

SUMMARY

1. The difficulties of an exact and objective determination of the QRS duration are discussed in detail.

2. The QRS complex usually has an isoelectric initial or terminal portion in some leads; the leads where QRS begins earliest are often not the same leads where it ends latest. The longest QRS duration, as measured in any single lead, may therefore be up to 0.02 second shorter than the duration from the first to the last point of QRS in synchronous leads. The differences are especially great if the precordial leads are used in addition to the limb leads for the measurement of QRS. In our own normal cases, the QRS duration, measured in synchronized limb and chest leads, usually exceeded the accepted normal upper limits.

3. There is at present no exact objective definition of the point where the QRS complex ends and the RS-T segment begins. The discrepancies in the definition of this point are especially great in the presence of a gradual transition between QRS and RS-T (wide RS-T junction); in this case they may reach 0.04 second. Several definitions and objective methods for the determination of the end of QRS are proposed and developed.

4. Definite criteria for the measurement of the QRS duration should be agreed upon as soon as possible. The chief purpose of this paper is to demonstrate the necessity and to indicate the general direction of such an agreement.

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THE VECTORCARDIOGRAM OF THE NEWBORN INFANT

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THIS report describes the characteristics of the QRS spatial vector loop of the normal newborn infant. It also discusses the effect of eccentricity on the recording of the vectorcardiogram in this age group.

METHOD

Vectorcardiograms were obtained from thirty-five normal newborn infants whose ages ranged from 3 hours to 7 days. They were recorded by means of the cube system of Sulzer and Duchosal as modified by Grishman and associates.[1,2] In this method four electrodes were placed on the trunk in such a way that Leads A, B, and C constituted horizontal, sagittal, and vertical lead axes, respectively (Fig. 1). A Cambridge Educational Cardioscope was used to visualize the loops of thirty infants. In the remaining five the loops were constructed from the Leads A, B, and C, which were registered simultaneously by a two-channel direct-writing electrocardiograph.

When the cardioscope was used, the component Leads A, B, and C were first visualized on the oscilloscope screen and the corresponding patterns copied on paper. The leads subsequently were combined to produce the frontal, horizontal, and sagittal loops, which were also copied from the screen. The direction of inscription was ascertained in three ways: (1) by direct observation as the loop was traced on the screen; (2) by opening the loop by sweeping it across the screen, and (3) by correlating the loop with the component leads. Only the QRS loops were studied because the P and ST-T loops were too small.

RESULTS

The QRS spatial loop in the normal newborn infant is usually located anteriorly, inferiorly, and mostly to the right. The initial part of the loop proceeds anteriorly, superiorly, and usually to the right for a short distance (initial arc). Then it swings downward, anteriorly, and slightly to the left (centrifugal limb) followed by a change of direction to the right, upward, and somewhat posteriorly (centripetal limb). The terminal portion frequently lies to the right, superiorly, and posteriorly to the isoelectric spot (Fig. 2,*A*).

The direction was always clockwise in the frontal plane, clockwise in the horizontal plane in thirty-three of the thirty-five cases, and clockwise in the

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sagittal plane in twenty-seven of the thirty-five cases. In two cases the horizontal loop inscribed a figure-of-eight (Fig. 2,*B*). In eight instances the sagittal loop was written counterclockwise (Fig. 2,*C*). In two cases the major part of the spatial loop was located superiorly (Fig. 2,*C*) and both times the centrifugal limb was inferior while the centripetal limb was superior (Fig. 2,*C*). Marked notching of the loops was not infrequent. Respiratory variations were seen often and on occasion caused striking transformations of the loops. Their analysis was not attempted.

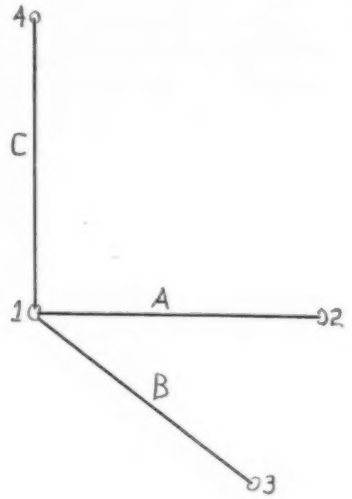

Fig. 1.—Diagram of cube system used in the recording of the vectorcardiogram. Electrode *1* is at the right posterior axillary line, *2* at the left posterior axillary line, *3* at the right anterior axillary line, and *4* suprascapular directly above *1*. Electrodes *1*, *2*, and *3* are at the level of the upper lumbar vertebrae. The bipolar leads are so poled that: Lead *A* equals 2 minus 1; Lead *B* equals 3 minus 1; and Lead *C* equals 1 minus 4. Lead *A* gives the horizontal component of the heart vector, Lead *B* the sagittal, and Lead *C* the vertical. The center of the heart (the origin of the heart vector) is theoretically equidistant from the four electrodes.

DISCUSSION

The spatial vector loop of the normal newborn infant is identical with that of older subjects with right ventricular preponderance. This confirms the traditional interpretation of the neonatal electrocardiogram as one of right preponderance.[5] The basic path of the spatial loop in right preponderance is first a short arc to the right and anteriorly, then a centrifugal limb to the left and down, followed by a centripetal limb to the right and up. Both latter limbs lie anteriorly. With lesser degrees of preponderance the centrifugal limb tends to lie more anteriorly than the centripetal, while with more severe degrees the centripetal limb is more anterior. The more severe the degree of preponderance, the more the spatial loop tends to lie to the right, anteriorly, and finally superiorly.[4] In the milder types the sagittal loop is inscribed clockwise; in the more severe types it is counterclockwise. In the newborn infant the sagittal loop is usually inscribed clockwise while in older subjects with congenital heart disease the direction is counterclockwise. However, some normal newborn infants

show loops that are in every way comparable to those seen in more severe degrees of right preponderance.

An important diagnostic feature in older subjects for the presence of right preponderance is a horizontal loop which lies anteriorly to the right and is clockwise. The vast majority of newborn infants also show this type of horizontal loop.

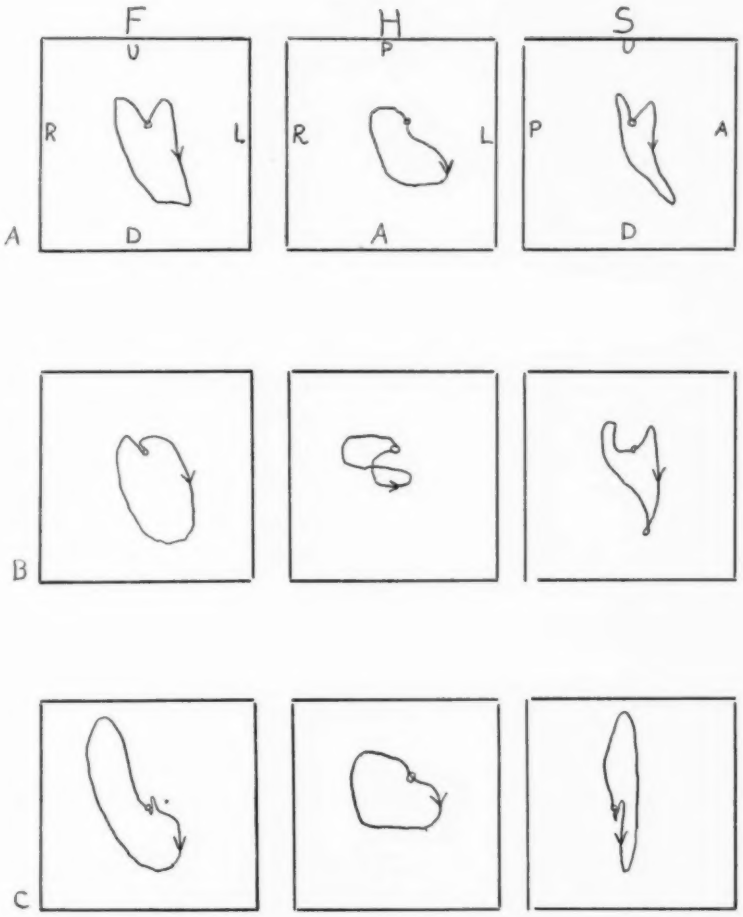

Fig. 2.—Drawings of different types of normal neonatal vectorcardiograms. Only the QRS loops are shown.

A, The most frequent type. All loops are inscribed clockwise. They are located mostly anteriorly, inferiorly, and to the right. There is a small terminal portion to the right, posteriorly, and superiorly.

B, An occasional variant. The horizontal loop describes a figure-of-eight.

C, A type of loop suggestive of marked right preponderance. The spatial loop is located for the most part superiorly; the sagittal loop is inscribed counterclockwise.

F, *H*, and *S* refer to the frontal, horizontal, and sagittal planes. *U* and *D*, *R* and *L*, and *A* and *P* indicate up and down, right and left, and anterior and posterior, respectively. Each set of loops consists of the three planes, and each plane has the orientation indicated in the top row.

It is important to realize that the normal newborn infant can show loops typical of marked degrees of right preponderance. This affects the ability of the method to reveal the presence of an abnormal degree of right preponderance

in newborn infants with congenital heart disease. At present one cannot distinguish between normal and abnormal right preponderance from a single electrocardiogram during the first few weeks of life.[6] However, a series of tracings taken over a period of weeks and months can be diagnostic. Normally the degree of right preponderance diminishes during the first few months of life. If the tracings show a persistance or even an increase of right preponderance then the diagnosis of abnormal right preponderance is justified. Vectorcardiography was so effective in diagnosing abnormal right preponderance in older subjects that it was expected to do the same for the newborn infant. The fact that the normal newborn infant can show a spatial loop with a marked degree of right preponderance indicates that even vectorcardiography will contribute little clinically to the solution of this problem.

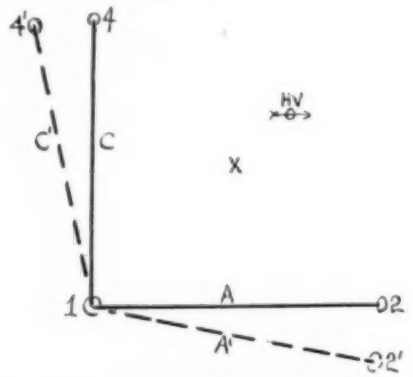

Fig. 3.—The effect of eccentricity on the axis of Lead *A* and of Lead *C*. *HV*, the heart vector, is situated near the left shoulder, away from *X*, the center of the geometric system. *HV* is closer to electrodes *4* and *2* than to *1*.

For purposes of projection, the directions of the effective axes of Leads *A* and *C* approximate the lines labelled *A'* and *C'*.

The loops recorded by the cube system in the newborn infant do not represent the heart vector accurately. Compared with Lead A, Lead C has a longer lead axis and Lead B a shorter lead axis. The contribution of Lead C to the loop will be too large and that of Lead B too small. This makes the loop elongated in the vertical dimension and flat in the sagittal. In addition the loops suffer a distortion because the heart of the newborn infant is so markedly eccentric.[7] The eccentricity of a heart vector with respect to a bipolar lead can change the effective axis of the lead. This was first demonstrated by Burger and van Milaan.[8] Later it was confirmed and elaborated by Wilson and associates[9,10] and also by Selvini and associates.[11]

If the heart vector is closer to one electrode of a bipolar lead than to the other, then the anatomic lead axis (a line connecting the two electrodes) is not the effective axis electrically. For purposes of projection, the effective axis can be geometrically portrayed by placing the anatomically closer electrode farther away from the heart vector and then placing the anatomically distal electrode closer to the vector.[8,11] As shown in Fig. 3, the effective axis of the lead is thereby

tilted. Anatomically, the electrical center of the heart is close to the left shoulder and would therefore be closer to the upper electrode of Lead C and to the left electrode of Lead A. Accordingly the effective axis of Lead C would be tilted so that its upper end would be more to the right than its lower end. Likewise the effective axis of Lead A would be so tilted that its left end would be lower than its right. The vector will be picked up differently by these skew axes as compared to the ideally orthogonal axes, that is, the vector would be projected differently on these skew axes. As a result the loops are distorted inasmuch as the plates in the cathode-ray tube are arranged as if the axes of the component leads are orthogonal. The eccentricity of the heart of the newborn infant is so unpredictable[7] that it appears impossible to correct for it clinically. Other systems for vectorcardiography would suffer as much from the eccentricity as does the cube system.

SUMMARY

1. The vectorcardiograms of thirty-five normal newborn infants were examined.

2. The spatial vector loop of the normal newborn infant is identical with that seen in older subjects with right ventricular preponderance.

3. Most neonatal loops are indicative of a mild degree of right preponderance but some show a more marked degree.

4 The effect of this finding on the problem of diagnosing abnormal right preponderance in the newborn infant is discussed.

5. The registered loops suffer a distortion due to the imperfections of the cube system and the eccentricity of the neonatal heart.

ADDENDUM

Since the above report was submitted we have found electrical left ventricular preponderance in two normal newborn infants, ages 1 and 5 days, respectively.

The electrocardiogram in the first week of life and again at the age of 1 month showed a positive QRS complex in aV_L. This confirms the original impression of the value of this lead for indicating the type of ventricular preponderance in the neonatal period.[5,6] The mean QRS vector lay between plus 40 and 50 degrees in both cases. The chest leads (V_{6R} to V_6) were not registered at the first examination. At the infants' age of 1 month, the QRS complex in the right chest leads was positive in one of the infants and biphasic in the other; in both infants, it was positive in the left chest lead.

The vectorcardiograms in both infants, registered by both the cube and tetrahedral systems, showed the pattern of left ventricular preponderance which is normal for the older age groups. The spatial loops lay to the left and inferiorly; the first part was located anteriorly and the second part posteriorly. The frontal and horizontal loops were inscribed counterclockwise; the sagittal loop was inscribed clockwise. The P and ST-T loops were directed downward and to the left. Re-examination of the infants at the age of 1 month revealed no abnormalities except for the persistence of the left preponderance in the electrocardiogram. No reliable blood pressure determination was obtained. More than 150 normal newborn infants have been examined by one of us (A.I.S.); these two have been the only ones with electrical left ventricular preponderance.

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ELECTROSTETHOGRAPHY. II.

New Method for Study of Precordial Transmission of Cardiodynamics

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THE METHOD herein described differs in so many details from current practices in phonocardiography that the term "new" has been used. In a study of vocal fremitus we described electrical equipment which eliminated the distortions due to stethoscopic attachments and recording systems with limited frequency response and suggested the use of the term "electrostethography" for equipment which was free from these sources of error.[1] The present method is a reapplication of some of these principles plus the development of a rapid and reliable calibration system which is basic to the problem of recording cardiodynamics.

The equipment consists of contact microphone, amplifier, electron to light converter, camera, and calibrating equipment. These will be briefly described together with results obtained.

METHOD

The microphones used were the Shure 66D* which are crystal type and designed for direct contact. Fig. 1 shows the shape of the frequency-output curve and it is to be noted that the output is essentially constant over the frequency range of 30 to about 700 cycles per second. The zone of increased sensitivity in the region of 300 cycles per second observed by Mannheimer was probably due to resonance in his pistonphone calibrater, since it was not found by us or the manufacturer.[2,3] The reduction in sensitivity below the 30 cycles is uniform for seven microphones studied and is determined in part by the time constant of the input stage of the amplifier. Seven of these microphones were studied intensively by us over a period of one year.[4] Here we will only summarize these observations: (1) the frequency-output curves are identical in shape to less than 5 per cent variation; (2) temperature variations of 15 to 35° C. do not alter significantly the shape of the frequency-output curve; (3) the microphone output is proportional to the driving force over the range of 2 to 100 dynes per square centimeter, and (4) ageing of the microphones did not alter the shape

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*Shure Brothers, Inc., Chicago, Ill.

of the frequency-output curve during this period. If the microphone is kept in a 50 per cent humidity environment when not in use, the output variation is less than 5 per cent.

This microphone thus has a quantitatively usable frequency range from about 10 to 1,000 cyc./sec. which our studies of over 600 cases have shown is an ample frequency range for heart vibration studies. The demonstration of the constancy of the frequency-output curve and the linearity of output justifies the rapid calibration technique to be described later, and makes feasible the use of multiple microphones for simultaneous recording.

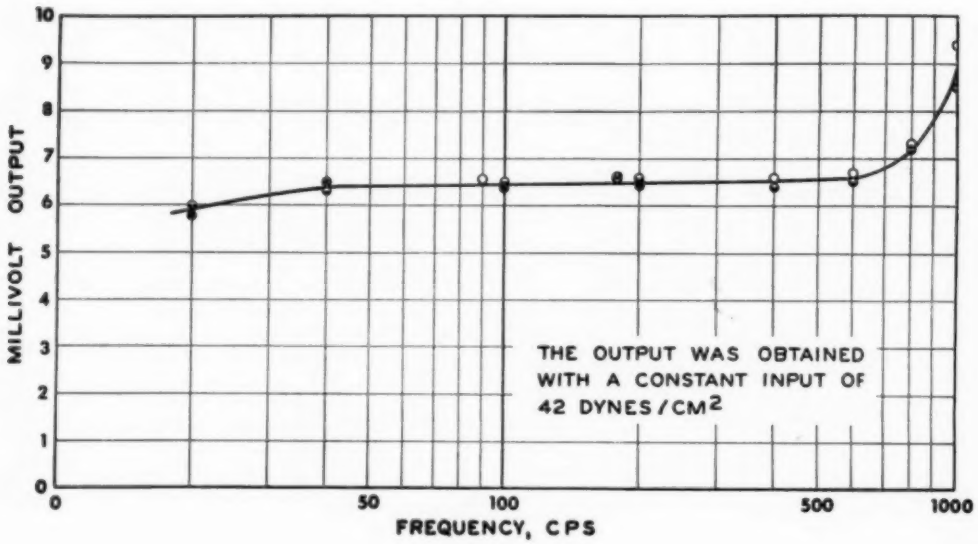

Fig. 1.

The amplifiers were conventional in design, push-pull in type, and resistance-capacity coupled. Frequency discrimination was determined by the time constant. This design results in predetermined low frequency cutoffs which are well adapted to the problem of cardiodynamic recording. Since an amplifier designed to include all of the frequencies from 10 to 1,000 cyc./sec. (the arbitrary limits of our range) will not produce a record of all of the heart frequencies present because of the high energy levels of the low heart frequencies which cause optical overshooting and blocking of the amplifiers, it is necessary to use a group of amplifiers which cut off varying portions of the lower frequencies.[2,5] In the early work of Einthoven, Thomas Lewis, and Frank, and even more recently when stethoscopic assemblies were used, these low frequencies were eliminated by vents in the pressure tubing assemblies or by the use of diaphragms of varying stiffness. Except in the few instances where the entire assembly was calibrated with a known source of vibration, such methods resulted in highly unpredictable frequency discriminations. Some of the potentialities using resonant chest pieces and resonant amplifiers have been developed by Rappaport and Sprague and later Wells, particularly in the recording of the normal and faint heart sounds.[6] Possi-

ble errors in band-pass filters of high resonance value such as were used by Mannheimer have been presented by Ljunggren and the criticism is proper in our experience.[7] An analysis of the dangers of resonance and proper filter design would be too technical for a clinical report but if an accurate record is desired of the forces present at the precordium then a careful consideration of these factors is necessary. Many earlier phonocardiographic records show resonance phenomena, that is, show oscillation of frequencies which in our experience were produced by resonant oscillations of the frequency of the recording equipment and which are frequencies that are not actually present at the precordium.

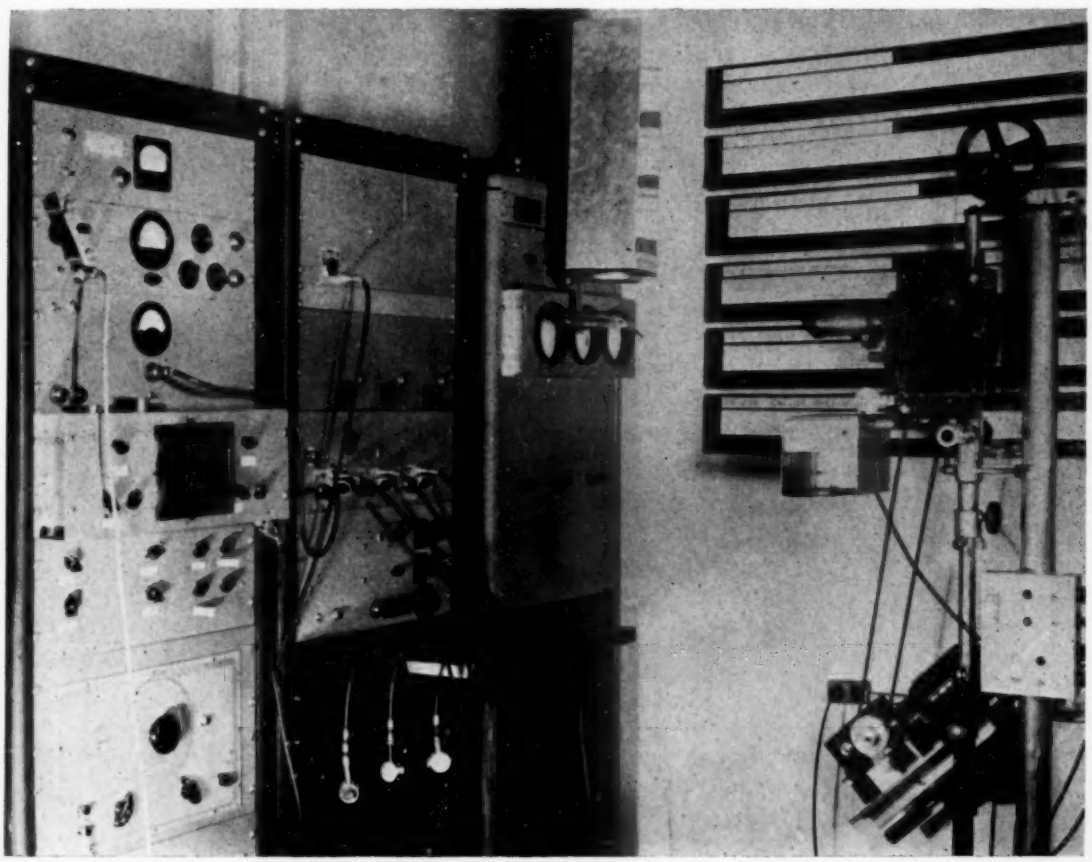

Fig. 2.

In the communications industry, where it is well known and extensively studied, this phenomenon is known as "ringing." With modern amplifier design it is not necessary to utilize resonating devices to gain sensitivity, and the resistance-capacity of cutoff filters used by us avoids ringing and permits a rigorous calibration technique.

The electron-light converters were 5CP-11 cathode-ray tubes. These were arranged as in Fig. 2, the vertical tube being used for the electrocardiogram.

The small spot size makes it an ideal photographic recorder, plus the fact that the deflection is proportional to the electrical input up to several millions of cycles per second. We have discussed elsewhere the limitations of galvanometer types of recorders.[8]

The camera used 6 cm. bromide paper and with an f 1.9 I lens ample exposure was obtained with the cathode-ray tube operated at low energy levels. Due to the long records a photostat attachment was included in the camera assembly using a turret head, right-angle prism, and illuminated box as can be seen in Fig. 2. The camera speed was 200 mm. per second, that is, four times faster than the usual phonocardiographic record. This speed was selected so that frequencies up to 1,000 cyc./sec. were measurable on the final record. For alignment purposes the magazine of the camera was removable so that a finely ground glass plate could be locked into the exact position of the paper emulsion. Three fine lines were engraved on this glass 0.5 mm. apart so that with suitable magnification the four beams of the cathode-ray tubes could be aligned to within 0.2 mm. equal to 0.001 second. The camera was driven by an induction motor of ample torque so that with the light load a constant slip was obtained and speed variation was not over 1 per cent. The grid of one cathode-ray tube was pulsed with a negative spike potential 60 times a second. This produced short blank spaces on the record at regular intervals so that the speed could be accurately checked.

The primary calibrating equipment has been described elsewhere.[9] The pistonphone provided an absolute standard and is used at the present time for occasional checks on the secondary calibraters. For the secondary calibrater a Western Electric 716-A receiver was substituted for the moving piston of the pistonphone as a source of power. This receiver has been designed for durability and stability and is held to close manufacturing tolerances and provides a rugged source for calibration. The source of power for driving the receiver is furnished by an audio-oscillator and this force is measured by a rectifier voltmeter with a suitable series resistance so that the meter reads directly in dynes per square centimeter. This calibrating equipment is assembled on a relay rack panel in the upper left-hand portion of Fig. 2. A quick clamp device holds the microphone in position. The calibrating procedure is as follows: (1) set the meter at the desired number of dynes, (2) clamp the microphone in position, and (3) adjust the gain of the amplifier until the desired deflection is obtained on the cathode-ray tube. Instead of actually measuring the deflections on the face of the cathode-ray tube, a Ferranti electrostatic voltmeter (third meter from the top in Fig. 2) can be switched to the horizontal deflection plates of each of the cathode-ray tubes and the amplifiers are then adjusted to the proper voltage. It should be emphasized that this method of setting the microphone is a direct setting and is not affected by temperature, humidity, or changes in the sensitivity of the microphone. Our studies demonstrating the constancy of the shape of the frequency-output curve, as noted previously, makes it necessary to set the microphone at only a single frequency, and we have used 100 cyc./sec.

For multiple microphone records three microphones are connected to separate amplifiers, as illustrated in Fig. 2. The patient is usually lying flat on the back and the microphones weighing 3 ounces are held in position by their weight and

a spring-clamp device which holds the microphone cable in position. The positions of the microphone are recorded in rectangular coordinates using the intersection of the midline and the second rib as x = 0 and y = 15 cm. A six-foot radiograph of the chest is taken with the subject lying flat on the back against the cassette and a rectangular grid placed on the front of the chest. Exposures are taken during quiet respiration or held at mid-respiration. To adjust the microphone to the proper sensitivity one microphone is moved around to various positions on the precordium until the desired sensitivity is obtained, that is, satisfactory deflection without overshooting. The microphone is then clamped to the secondary calibrater and the number of dynes recorded. The three microphones are then all adjusted to the same sensitivity, using a near unit such as 2, 5, or 10 dynes per centimeter deflection on the photographic record.

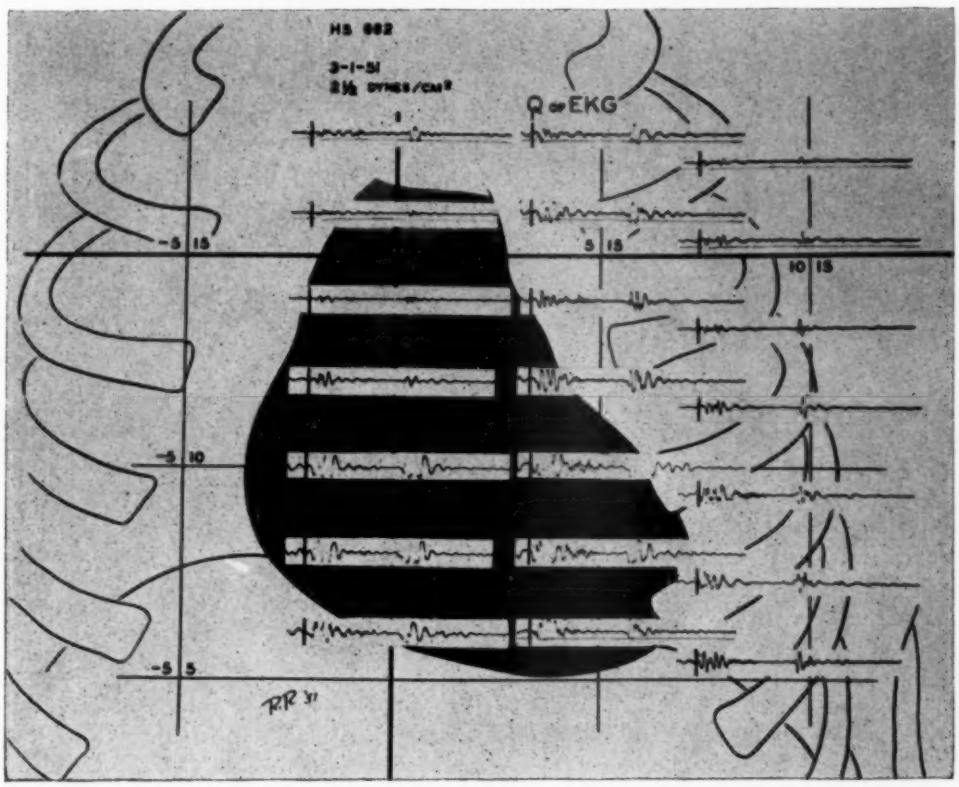

Fig. 3.

Usually twenty to thirty different positions are recorded and the individual records include four or more respiratory cycles because of respiratory variations in the wave form of the sounds and murmurs. For detailed study, selected heart cycles are mounted upon a three-times enlargement of the individual heart outline, the position of the Q wave of the electrocardiogram being marked on each trace. Although each trace is located by rectangular coordinates which correlate to the chest grid, it is difficult to visualize easily this large mass of data; the layout illustrated in Fig. 3 is of great help. Furthermore, by the use of heart

models, the results of fluoroscopy, and post-mortem studies, further details of the heart structure can be located on the heart outline providing further material for analysis. Since the calibrated method is accurate to about 5 per cent for amplitude, it is possible to study the transmission of sound and murmurs over the precordium. Timing precision is of the order of a few thousandths of a second so that the earliest appearance of many of the vibrations can be located. The frequency characteristics of a sound or murmur permit its identification in different areas so that combinations of sounds can be separated. These distinctions are at times easily apparent but can be studied accurately if a tracing is made on a transparent sheet and this tracing overlaid on other waves for comparison.

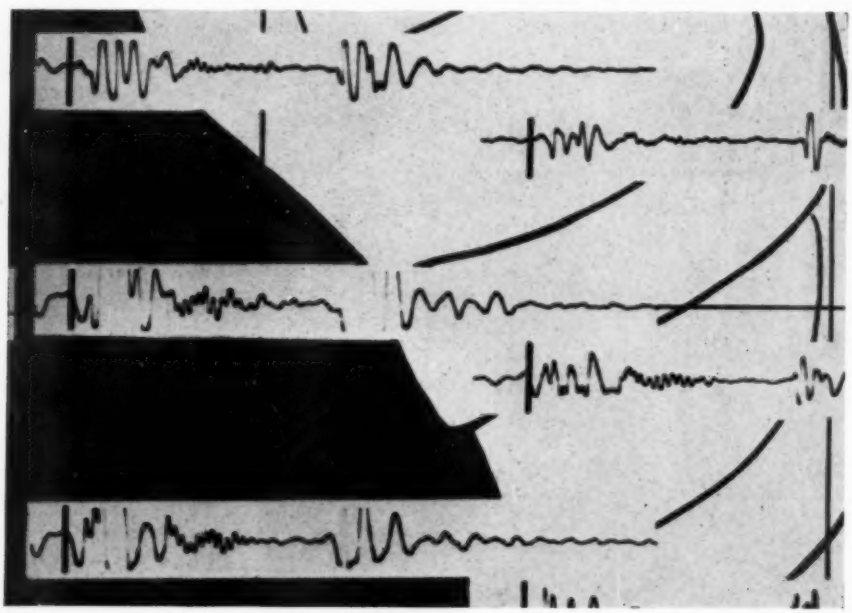

Fig. 4 (HS 662).—Closeup of left border of heart and chest. Heavy vertical line on each tracing marks the time of the Q wave of Lead II of the electrocardiograph. This is followed by the first heart sound vibrations and, after a close interval, the functional murmur occurs, which is relatively constant in frequency and ends definitely before the second heart sound vibration.

In the method of precordial study just described a single amplifier is used for each microphone. Several sets of amplifiers are available with different low frequency cutoffs. However, if a frequency analysis of the sounds or murmurs is desired in more detail, then a single microphone is used and the signal is passed through three amplifiers with a low, a middle, and a higher frequency cutoff. Over-all calibration is accomplished as previously reported except for the substitution of the amplifier with the desired cutoff.[9]

RESULTS

About eighty cases have been studied by the multiple microphone technique which has been available for a year. The single-microphone, three-amplifier method for frequency separation has been used in about 600 cases. The following cases selected are to demonstrate the method.

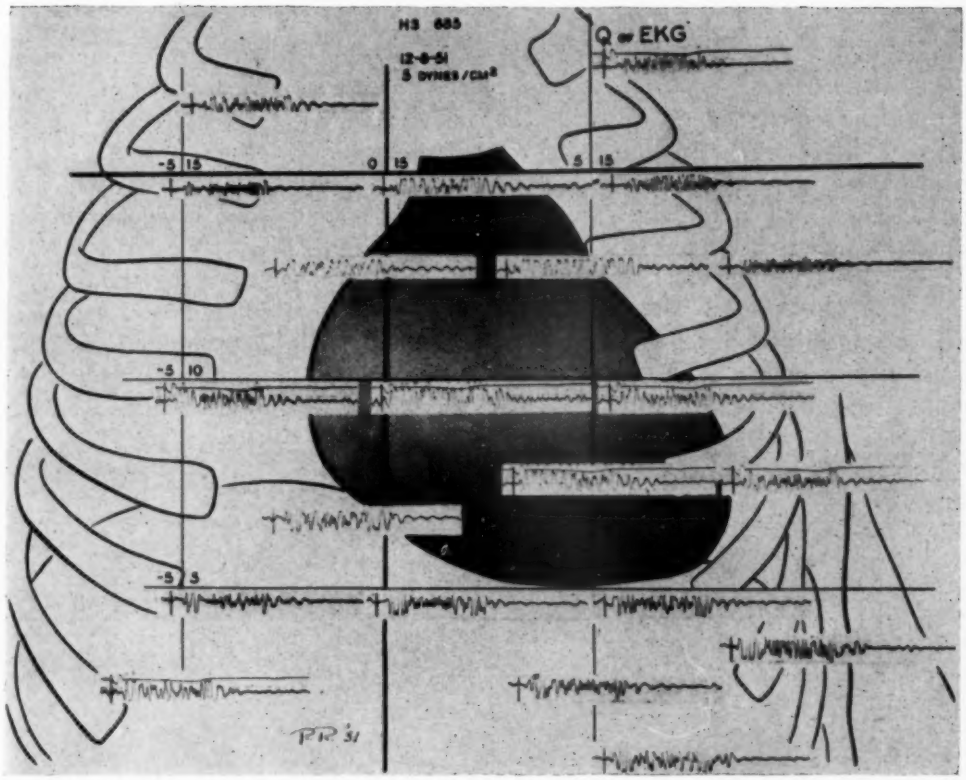

Fig. 5.

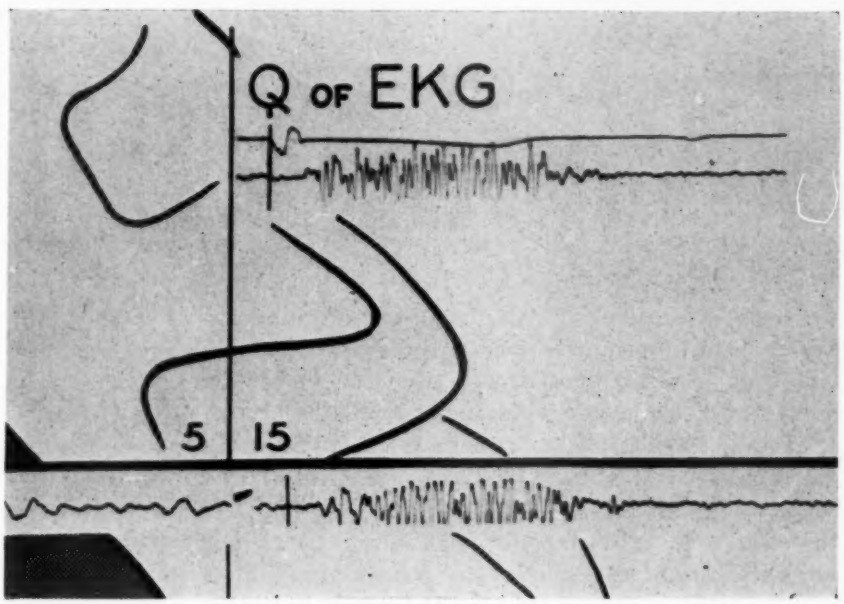

Fig. 6.—Closeup of upper left portion of Fig. 5.

HS 662.—Fig. 3 is a layout of the recordings from a young adult with a functional systolic murmur. Because of the marked reduction a closeup along the left border of the heart is shown in Fig. 4. Each recording represents a complete heart cycle and the vertical black line marks the beginning of the Q wave from Lead II. Shortly after the Q wave the vibrations of the first sound began. Following the first sound there was a murmur which was uniform in frequency and ended well before the onset of the second sound. The frequency in our present series of twelve cases varied between 90 and 120 cyc./sec., and the distribution of the murmur to the left of the sternum has been characteristic.

HS 620.—Fig. 5 is the layout and Figs. 6 and 7 are closeups of a patient with congenital heart disease about whom there was disagreement as to whether one or two murmurs were present. Two shunt-type murmurs are shown: the one in the upper left portion of the chest was of high and mixed frequencies while

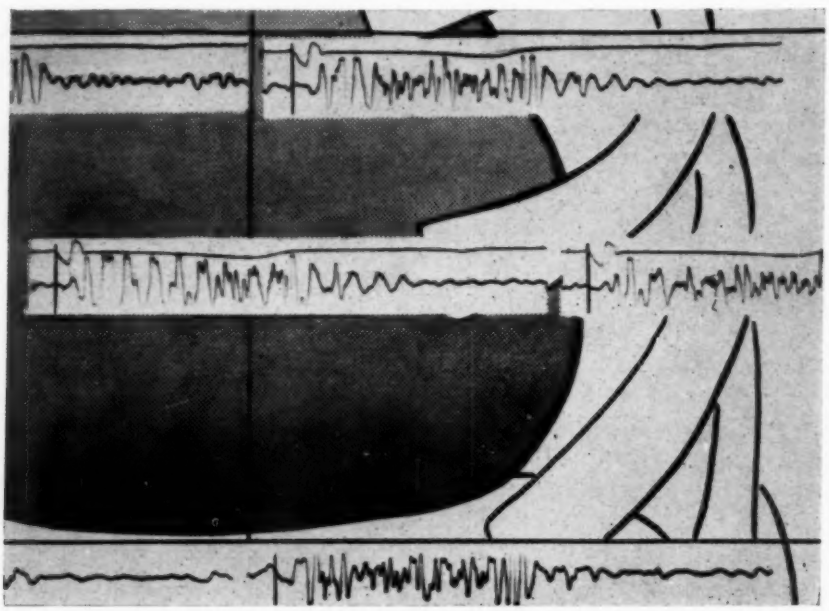

Fig. 7.—Closeup of lower cardiac area from Fig. 5.

the one in the region of the ventricles of the heart was louder and of lower frequencies and, in addition, showed an axis of transmission that was comparatively transverse. Both murmurs persisted through the second sound which in many areas was impossible to identify by simple visual inspection. At the present time the frequency pattern of the lower murmur is interpreted as a ventricular shunt since, to date, auricular septal leaks have shown murmurs of such low frequency that the record gives much more evidence of a leak than can be heard by stethoscope.

HS 684.—Fig. 8 is from an adult with a small heart and an extensively calcified pericardium. This shows a grossly apparent third sound closely following the second sound with an abnormally wide distribution as compared

with our third sounds recorded in young adults and in cardiac enlargement associated with hypertension. This is the most striking example of a third sound in our files, both in amplitude and wideness of distribution. The relatively simple wave form of the third sound in our studies suggests that from a vibrational standpoint it could well be due to the filling phase of the heart reaching some maximal state, such as the elastic confines of the pericardial sac. In this particular case the third sound disappeared almost entirely following surgical removal of the calcification which was accomplished without rib resection.

Figs. 9 and 10 are frequency separation records from a normal adult and a patient with mitral valve stenosis. The top trace includes the low frequencies. The electrocardiograph is between the top and middle frequencies and the bottom frequency has the low and middle frequencies filtered out, leaving residual high frequency elements. These figures illustrate the differences when the same heart

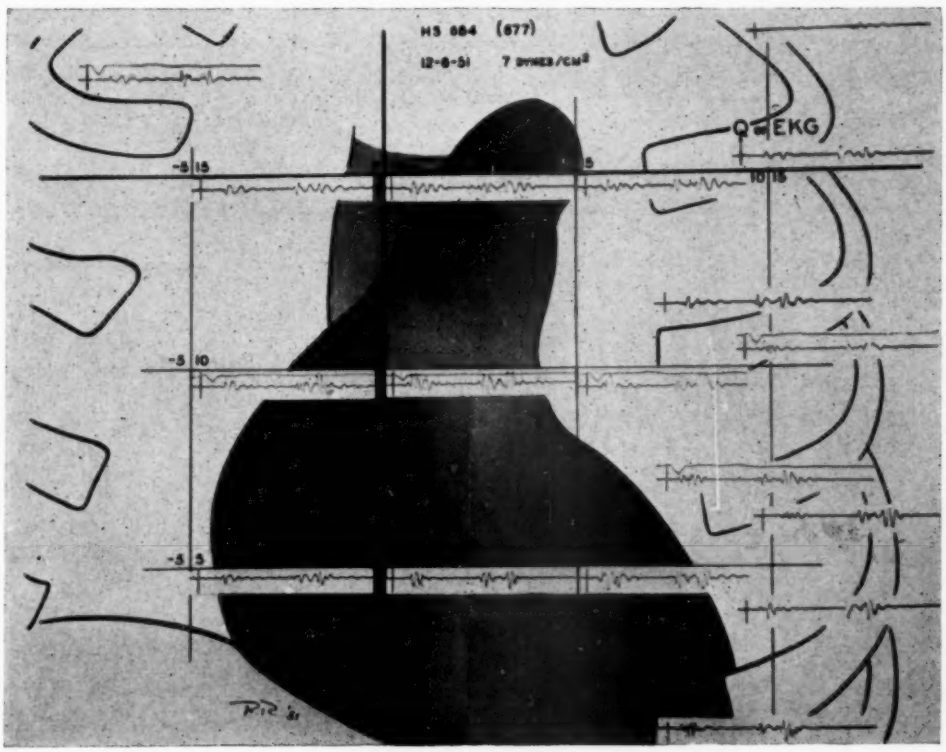

Fig. 9.

cycle is recorded with increasing portions of the low frequencies omitted. The complexity of the systolic murmur in Fig. 10 is readily apparent by comparing the differences in the three traces. By using resonant band-pass filters, such as used by Mannheimer, or the use of resonant chest pieces and stethoscopic attachments, it is easily possible to design phonocardiographs which will record the systolic murmur, such as in Fig. 10, and essentially miss the diastolic murmur, or vice versa. The use of R-C or cutoff filters and multiple recording permits

accurate calibration and avoids resonance phenomena. Space does not permit illustrating a long strip of record but the traces superimpose when the subject is properly relaxed, when similar phases of respiration are compared, when marked variations in rate do not occur, and when severe myocardial disease is absent.

DISCUSSION

The present method involves a direct conversion of the vibration at the precordium to an electrical impulse which can be amplified and converted to a light deflection by apparatus that is rugged and dependable and subject to calibration by well-standardized procedures. The addition of the pistonphone and the secondary calibrater adds the necessary calibration at the input so that the over-all method errors can be held within 5 per cent variation and can be improved by further refinement. The use of the crystal microphone, together

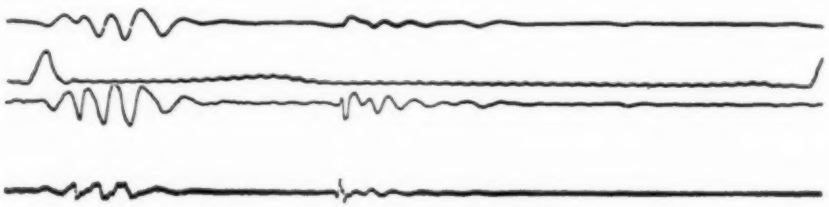

Fig. 9.—The top tracing is the low frequency record: the second line is the electrocardiogram with the QRS at the extreme left. The third line has the lower frequencies attenuated, and the bottom line has the lower and middle frequencies attenuated.

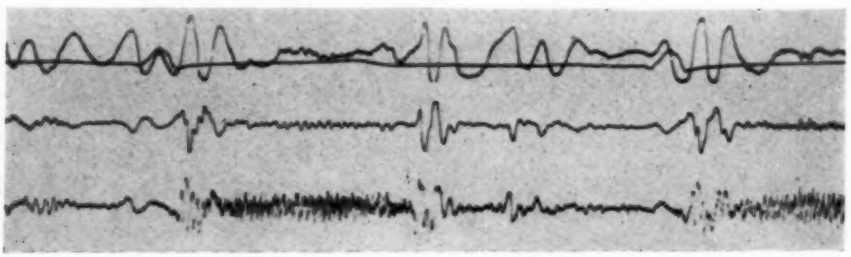

Fig. 10.—Frequency selector record from a case of mitral valve stenosis. The electrocardiogram is partially covered by the low frequency trace at the top but its components can be identified. Note the marked differences in characteristics in the systolic murmur in the different frequency channels showing the complexity of the murmur structure and contrast this with the lower frequency pattern of the diastolic murmur with a well-defined third sound.

with the circuit constants employed in the input stage, limits the low frequency response of the equipment so that the microphone does not respond to slow variations such as the gross heart beat and respiration, or static pressure. The method being a direct application of vibrational analysis, in contrast to phonocardiography, permits a study of the timing of various components of the cardiac cycle and an evaluation of strains and abnormal activity. The sensitivity of the method is in contrast to the slow frequency response obtained in measuring pressure changes through long and narrow catheters. The multiple microphone tech-

nique permits simultaneous study of the same heart cycle in different areas of the precordium. In comparison with electrocardiography, the records are much more complex but the records are direct results of cardiodynamics and are not action potentials. Although the method in its present quantitative form provides useful information, it will be necessary to reidentify the various phases of the cardiac cycle by their characteristic patterns before one can talk in terms of ejection times, pressure times, and abnormal dissociation of parts of the cardiac cycle.

SUMMARY

1. The method involves direct conversion of the cardiac forces at the precordium into electrical impulses, followed by amplification and conversion to light deflections by electrostatic means.

2. Calibration is in absolute units, and conditions for predictable operation have been determined and applied to the development of a method applicable to clinical study.

3. Some of the results of precordial study using multiple identical microphones are presented.

4. The method is applicable to the study of cardiodynamics as transmitted to the precordium and prompts a reidentification of various phases of the cardiac cycle in the normal and diseased heart.

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THE EFFECT OF DIGITOXIN ON THE ELECTROCARDIOGRAM

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ELECTROCARDIOGRAPHIC changes in normal human beings after digitalis have been studied by several investigators.[1-3] Changes listed include P-R lengthening, A-V dissociation, QRS widening, Q-T_e shortening, J and S-T depression, T inversion and appearance of ectopic foci.

It has been our purpose to study the electrocardiographic effects in normal human beings of doses of digitoxin equivalent to those which usually produce some electrical and physiologic change in decompensated hearts, and to assay the relative importance of the effects found in the recognition of digitalis effect in a single tracing.

METHODS

Digitoxin (1.2 mg.) was given to forty normal subjects, 20 to 30 years of age, after a control tracing. An additional 0.4 mg. was given the next day to twenty-two of the subjects. In addition, thirteen other subjects were given placebo tablets and the same routine followed. Also, the electrocardiograms of fifteen patients who had been digitalized for congestive heart failure with similar amounts of digitoxin were selected from hospital files and analyzed for comparison.

Control 24-hour and, in the twenty-two subjects receiving the second dose, 48-hour tracings were taken. Standard leads, augmented limb leads, and six precordial leads were recorded photographically with a string galvonometer electrocardiograph. The tracings were read by two observers without knowledge of the drug status. The P-R interval was read in standard Lead II. The T wave of maximum amplitude was measured. The Q-T, RR, and QRS were measured in the same lead. The rate was determined from the RR; the Q-T_e was calculated using Bazett's formula ($Q\text{-}T_e = Q\text{-}T/\sqrt{RR}$).

The changes after drug administration were statistically analyzed. Using each subject as his own control, pairing was used to avoid the effects of wide variations of T amplitude and rate normally present. For each variable, the standard deviation of the mean difference, that is, the standard error, was calculated, then the Fisher's "t" value, and from this the probability of chance variation was determined. Only changes with less than one chance in 100 of being random have been considered significant.

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RESULTS

In Tables I to V, the distribution of changes is listed. The mean difference, "*d*," the standard error, "*sd*," Fisher's "*t*" value, and the probability of the changes being random, "*P*," are indicated.

40 DIGITALIZED NORMALS AT 24 HOURS

	$\bar{d}$	$s\bar{d}$	t	P
RATE PER MIN	-5	±1.74	2.88	<.01
PR SEC	+.01	±.004	2.5	>.01
QRS SEC	+.0015	±.002	.75	>.1
QTc SEC	-.019	±.0055	3.43	<.01
T MM	-1.2	±.41	2.9	<.01

Table I.—Changes in the electrocardiograms of forty normal subjects 24 hours after 1.2 mg. digitoxin. *d*, Mean change; *sd*, standard deviation of the mean change (standard error); *t*, Fisher's "t" factor, and *P*, probability that changes are due to chance.

22 DIGITALIZED NORMALS AT 48 HOURS

	$\bar{d}$	$s\bar{d}$	t	P
RATE PER MIN	-2	±2.9	.69	>.1
PR SEC	+.01	±.007	1.4	>.1
QRS SEC	-.0005	±.0084	.06	>.1
QTc SEC	-.024	±.0084	2.86	<.01
T MM	-2	±.39	5.1	<.01

Table II.—Changes in the electrocardiograms of twenty-two normal subjects 48 hours after 1.6 mg. of digitoxin (1.2 mg. immediately, 0.4 mg. at 24 hours). *d*, Mean change; *sd*, standard deviation of the mean change (standard error); *t*, Fisher's "t" factor, and *P*, probability that changes are due to chance.

There was no statistically significant change in conduction in normal subjects given digitalis, as reflected in P-R or QRS duration at either 24 or 48 hours (Tables I and II). In five subjects the P-R was prolonged more than 0.04 second, 24 hours after digitoxin, and their heart rates were also slowed more than the mean of five per minute. One subject demonstrated the Wolff-Parkinson-White syn-

drome, which was unaltered by digitoxin. One subject had many single nodal escape beats in the control tracing. Twenty-four hours after 1.2 mg. of digitoxin, there were runs of nodal escape beats and a P-R or 0.21 second in the beats of sinus origin. Not only was depolarization not prolonged but its order was not changed, as shown by constancy of QRS patterns throughout the tracings in all the subjects studied. The P-R and QRS intervals were unchanged in the tracings of decompensated hearts.

15 DECOMPENSATED PATIENTS

	$\bar{d}$	$s\bar{d}$	t	P
RATE PER MIN	-13.9	±2.5	5.6	<.01
PR SEC	+.01	±.009	1.1	>.1
QRS SEC	-.0007	±.0029	.078	>.1
QTc SEC	-.049	±.008	5.8	<.01
T MM	-3.1	±.91	3.4	<.01

Table III.—Changes in the electrocardiograms of fifteen patients digitalized for decompensation with 1.2 to 1.5 mg. on first day and 0.1 mg. or 0.2 mg. per day for three to eight days thereafter. *d*, Mean change; *sd*, standard deviation of the mean change (standard error); *t*, Fisher's "t" factor, and *P*, probability that changes are due to chance.

CONTROL (PLACEBO) GROUP AT 24 HOURS

	$\bar{d}$	$s\bar{d}$	t	P
RATE PER MIN	+1.92	±3.01	.64	>.1
PR SEC	+.0054	±.0037	1.46	>.1
QRS SEC	-.0023	±.0017	1.35	>.1
QTc SEC	+.0006	±.0117	.05	>.1
T MM	-.192	±.372	.52	>.1

Table IV.—Changes in the electrocardiograms of thirteen normal subjects given placebo tablets prepared to resemble digitoxin at 24 hours. *d*, Mean change; *sd*, standard deviation of the mean change (standard error); *t*, Fisher's "t" factor, and *P*, probability that changes are due to chance.

As expected, significant changes were found in repolarization. In normal subjects, even at the low dosage used, there was a significant lowering of T waves and significant shortening of Q-T_c at 24 and 48 hours (Tables I and II).

Detectable S-T change was found in only four of the forty normal subjects, none over 1.5 mm.; three of the four were concordant shifts, opposite the usually expected discordant shifts.

Maximum amplitude of the T wave was found in the same lead as before in all but two normal subjects and in all the decompensated hearts, suggesting a minimal shift in the axis of repolarization.

The patients digitalized for failure showed significant T wave lowering (Table III) but not shortening of the Q-T_e when tracings 48 hours after digitalization were selected. However, when tracings taken after remission of extracardiac complications in three of these patients were used, significant Q-T_e shortening was found for the whole group (Table III).

S-T segment change was found in five of the fifteen patients, all classically discordant, ranging from 0.5 to 3.0 mm.

Change in the heart rate of normal subjects 24 hours after 1.2 mg. of digitoxin was significant (Table I). However, the twenty-two subjects given an extra 0.4 mg. of digitoxin failed to show credibly slower rates at 48 hours compared to the control (Table II). Slower rates after digitalis was the rule in the patients with congestive failure (Table III).

CONTROL (PLACEBO) GROUP AT 48 HOURS

	$\bar{d}$	$s\bar{d}$	t	P
RATE PER MIN	-5.85	±3.1	1.89	>.05
PR SEC	+.0015	±.001	1.5	>.1
QRS SEC	+.0023	±.0026	.88	>.1
QTc SEC	+.0026	±.0124	.21	>.1
T MM	0	0	0	∞

Table V.—Changes in the electrocardiograms of thirteen normal subjects given placebo tablets prepared to resemble digitoxin at 48 hours. *d*, Mean change; *sd*, standard deviation of the mean change (standard error); *t*, Fisher's "t" factor, and *P*, probability that changes are due to chance.

Before any drug, premature beats were noted in two normal subjects, one of auricular origin, the other of A-V nodal origin. After digitoxin the subject with auricular premature beats showed none. Nodal premature beats increased in the other subject after digitoxin. Also, four additional subjects showed ventricular premature beats after 1.2 mg. of the drug, although none were present in their control tracings. Of these four subjects with beats of ventricular origin, two were also in the group which showed marked P-R prolongation and rate decrease.

In the thirteen subjects given placebo tablets, there was no statistically significant change in any of the measured elements of the electrocardiogram, rate, P-R, QRS, T, or Q-T_e (Tables IV and V).

DISCUSSION

It seems incontrovertible that digitoxin, and presumably other digitalis preparations, has its most important electrical effect on the repolarization process (T wave). It has been assumed[3] that relatively small doses of digitalis may change the S-T and T segments of abnormal hearts but not of normal hearts, although Q-T_e shortening in normal hearts has been repeatedly observed.[2-4] Toxic doses of digitalis have been observed to cause conduction and rhythmicity changes in normal as well as abnormal hearts.[1]

These data indicate that digitalis produces an entirely analogous effect on normal and abnormal hearts' repolarization. The onset of this process is accelerated in those parts of the heart where it is normally last to appear. This tends to abolish the ventricular gradient and to shorten the entire electrical cycle. How this is accomplished is as unknown as the reason for having a ventricular gradient at all.

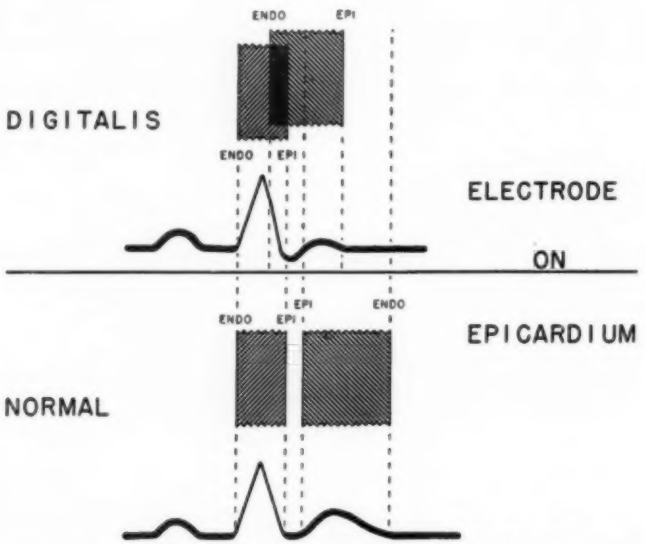

Fig. 1.—Diagram illustrating temporal relation of electrocardiographic deflections and electrical phenomena in the various portions of the ventricular wall.

As shown in Fig. 1, the order of repolarization is reversed, inverting the T wave. Endocardial repolarization, usually last, is accomplished early, thus shortening the electrical cycle. If repolarization overlaps depolarization as shown by overlapped shaded areas in the figure, the junction is depressed. The effect on the order of repolarization may not be apparent in a single tracing of a normal subject because it may be too small to invert the T wave, and mere lowering passes unnoticed. Most decompensated hearts have already lost some

ventricular gradient, that is, their T waves are lower or even inverted. Further loss of gradient either inverts a small upright T which is easily noticed or, if already inverted, depresses the S-T segment and junction, also easily noticed.

While the changes in repolarization in normal subjects, and decompensated patients appear to be in the same direction, they may not be of equal amount. Since recovery from decompensation may itself affect the order of repolarization in addition to the digitalis given, comparison of repolarization changes in normal subjects and patients in failure would not be valid and has not been attempted.

These data would indicate no constant effect of digitalis on conductivity in normal or abnormal hearts at the dosage levels used. Others[1,3] have shown that conduction will be profoundly affected in all hearts if enough digitalis is given. The wide range of P-R change in the data presented here indicates that, even more than with repolarization, there is considerable variation in individual hearts, normal or abnormal, in their conductivity response to digitalis.

The significant rate decrease in normal subjects 24 hours after digitoxin was probably not due to decrease in apprehension since those given placebo tablets failed to show it. One cannot be sure of this since separate groups of subjects were used. Since there was no significant rate change in those followed for 48 hours, one suspects that slowing of rate at this dosage is a matter of individual reaction to the drug. Elimination of the five subjects who showed ectopic beats and unusually long P-R intervals after digitoxin abolished the significant rate decrease at 24 hours. A larger series, with increasing amounts of the drug over a longer period of time, would define better the range of rate change, if there is one. The slowing of rate in decompensated hearts is attributable to loss of stimuli causing tachycardia as output improves, as well as to an effect of digitalis on sinus rhythmicity.

Ectopic beats appearing after digitoxin are apparently a matter of individual sensitivity since they appear only sporadically at these dosage levels, and then more often in hearts whose rate has been slowed more than an average amount.

SUMMARY

This study would indicate that digitoxin changes the order of repolarization in a predictable manner though in an unpredictable amount in both normal and abnormal hearts. The changes in S-T and T as well as Q-T_e are best explained by acceleration of repolarization in subendocardial muscle, thus abolishing the normal ventricular gradient. Digitoxin effect on conductivity, rate, and rhythmicity is less predictable in normal hearts, individual response varying greatly.

We acknowledge the assistance of Dr. Richard H. Lyons.

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ANTICOAGULANT THERAPY IN ACUTE MYOCARDIAL INFARCTION

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SINCE the advent of anticoagulant therapy in the treatment of acute myocardial infarction, there has been much discussion as to its value as an adjunct form of therapy. The possibility of preventing extension of coronary thrombosis and the development of mural thrombi was first advocated by Solandt, Nassim, and Best,[1,2] following animal experimentation using heparin. However, only after the identification and synthesis of Dicumarol were these observations applied to man on a significant scale. The reports of Wright,[3,4] Nichol and Page,[5] Peters, Guyther, and Brambel,[6] and others[7-9] were very favorable. Wright and associates[10,11] under the auspices of the American Heart Association, presented the report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction which gave substantial support to this form of treatment. In recent months, however, several reports[12-14] and a critique[15] appeared which are not as favorable, questioning the value of the routine use of anticoagulants in the treatment of myocardial infarction.

In order to determine the efficacy of anticoagulant treatment for acute myocardial infarction in a general hospital, a controlled study was undertaken under the observation of a specialized anticoagulant team. The team consisted of two consultants, two residents, and a full-time laboratory technician. The consultants saw each case, confirmed the initial diagnosis clinically and electrocardiographically, and observed the progress of the patient. Those cases in which the diagnosis of acute myocardial infarction was equivocal either clinically or electrocardiographically were excluded from this study. The residents of the team saw each patient daily, prescribed the required dosage of the anticoagulant, observed for complications, and noted the progress. Thus the mode of treatment at all times was in the hands of the two residents of the team rather than that of the general house staff. The technician performed the prothrombin tests and the Lee-White clotting times.

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METHODS AND MATERIAL

The cases included in this study were obtained from the medical wards of Cook County Hospital, being referred to the anticoagulant team by the ward physician. Each patient was seen shortly after notification, and alternate cases were placed in the treated and control groups, respectively. This classification into the two groups was strictly adhered to except for those patients who, when first seen, were immediately placed in a special group. The latter group included those patients who were in the hospital ten days or more before the team was notified or in whom a contraindication to anticoagulant therapy existed, such as blood dyscrasia, gastrointestinal ulceration, hepatic or renal diseases. This latter classification was thought necessary in order to compare the treated and control groups under as unbiased conditions as possible.

The prothrombin time was performed according to the method of Quick,[16] utilizing thromboplastin freshly prepared in our laboratory by acetone extraction of human brain, 0.0125M calcium chloride, and 1.34 per cent sodium oxalate solution as an anticoagulant for the blood specimens. The technician drew all daily blood samples for the tests employed. For the prolonged anticoagulant therapy Dicumarol was administered according to accepted standards maintaining the prothrombin activity between 10 and 30 per cent. Heparin in intermittent intravenous injections was used in those cases in which immediate anticoagulant effect was deemed necessary. Tromexan* (brand of ethyl biscoumacetate) was used in place of Dicumarol in ten of our treated cases. Treatment was continued for a period of thirty days or longer.

TABLE I. SEX AND AGE DISTRIBUTION

AGE (YEARS)	TREATED		CONTROL		SPECIAL	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
30 to 39	1	2	3	0	2	0
40 to 49	4	2	8	0	6	0
50 to 59	18	9	12	6	4	1
60 to 69	18	6	20	9	10	4
70 and over	4	7	7	5	3	3
Unknown	2	3	5	1	4	
Total	47	29	55	21	29	8
Average Age	58.8	60.3	58.8	65.6	58.0	68.0

*Tromexan was supplied through the courtesy of Geigy Company, Inc., New York, N. Y.

RESULTS

Our series consisted of a total of 189 cases of acute myocardial infarction, of which seventy-six were in the treated group, seventy-six in the control group, and thirty-seven in the special group. The results were subjected to statistical analysis using the Yates modification of the chi square methods.* Such factors in the two groups as age, sex, hypertension, previous myocardial infarction, and history of angina were subjected to statistical analysis in order to determine whether significant differences occurred in the treated and untreated cases.

The age and sex distribution is shown in Table I. The majority of patients were in the 50- to 70-year age group, and the average age of men and women was similar. The sex distribution in the two major groups did not differ significantly.

Tables IIA and IIB show the incidence of hypertension, which when examined by the chi square test showed a probability of one in three of a chance occurrence. The mortality in twenty-four treated hypertensive patients was nine as compared with five deaths of seventeen control subjects. This closely paralleled the findings in the nonhypertensive group in which there were fourteen deaths in fifty-one treated patients and eighteen deaths in fifty-five control subjects. All four thrombo-embolic phenomena in the treated series occurred in the nonhypertensive group, while in the control series two patients with thrombo-embolism had hypertension and four did not. This suggests that hypertension does not affect the mortality or the occurrence of thrombo-embolism in either of the two groups.

Comparison of patients with a history of previous myocardial infarction (Tables IIA and IIB) showed a similar incidence in the treated and control groups. There were three deaths in each group, though a history of previous infarction was obtained in four patients in the treated and seven in the control group. No thrombo-embolic phenomena occurred in patients who gave a history of previous myocardial infarction.

The incidence of angina was found to vary significantly between the two groups, being more frequent among men of the treated group (Table IIC). The mortality in eighteen treated patients with a previous history of angina was ten as compared with five deaths in thirteen control patients. In the group without a history of previous angina there were thirteen deaths in thirty-four treated patients and eighteen deaths in thirty-five control patients. Further analysis of the mortality in men with angina shows no difference in the treated and control series (Table IIC). Thrombo-embolic phenomena in the treated series occurred in two patients having a history of angina and in two patients without such a history while in the control series all six episodes of thrombo-embolism occurred in the nonangina group. Two of these patients were women and were in the nonangina control series.

The over-all mortality was identical in the two series (Table III). When further separated into the time of death prior to and after forty-eight hours the mortality is found to be slightly less in the treated series after forty-eight hours

*Statistical analysis was done by Dr. Robert Schrek, Veterans Hospital, Hines, Ill.

TABLE IIA. HISTORY OF PREVIOUS DISEASE

	TREATED		CONTROL		SPECIAL	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Hypertension	11	13	10	7	4	2
Angina	21	7	10	8	5	2
Previous myocardial infarction	4	0	5	2	3	2

TABLE IIB. INFLUENCE OF HYPERTENSION AND PREVIOUS MYOCARDIAL INFARCTION ON MORTALITY AND THROMBO-EMBOLISM

	HYPERTENSIVES		NON-HYPERTENSIVES		PREVIOUS INFARCTION		NO PREVIOUS INFARCTION	
	TREATED	CONTROL	TREATED	CONTROL	TREATED	CONTROL	TREATED	CONTROL
Deaths	9	5	14	18	3	3	20	20
Living	15	12	37	37	1	4	51	47
Total*	24	17	51	55	4	7	71	67
Thrombo-embolism	0	2	4	4	0	0	4	6

TABLE IIC.

	TREATED		CONTROL	
	MEN	WOMEN	MEN	WOMEN
A. HISTORY OF PREVIOUS ANGINA. MORTALITY AND THROMBO-EMBOLISM				
Deaths	6	4	3	2
Living	15	3	7	6
Total*	21	7	10	8
Thrombo-embolism	2	0	0	0
B. NO HISTORY OF PREVIOUS ANGINA. MORTALITY AND THROMBO-EMBOLISM				
Deaths	8	5	15	3
Living	18	16	25	10
Total	26	21	40	13
Thrombo-embolism	2	0	4	2

*Totals do not equal seventy-six in each group because of lack of reliable history in some cases.

but this is statistically insignificant. Thrombo-embolic complications occurred in six patients in the control series and four patients in the treated series (Table IV). Of these, two in the treated and three in the control series were the immediate causes of death. One patient in the treated series had a pulmonary infarction prior to admission to the hospital but no subsequent thrombo-embolism.

In the treated series, treatment was started within forty-eight hours after infarction in forty-nine patients and between forty-eight hours and ten days in twenty-seven patients. Bleeding, manifesting itself as epistaxis, ecchymosis, gross and microscopic hematuria, occurred in four patients. None was of sufficient severity to require specific treatment or cessation of anticoagulant therapy.

TABLE III. MORTALITY

	PATIENTS		
	TREATED	CONTROL	SPECIAL
Died within 48 hours	9	6	2
Died after 48 hours	14	17	7
Total Mortality	23	23	9
Lived	53	53	28
Total	76	76	37

TABLE IV. PATIENTS WITH THROMBO-EMBOLIC PHENOMENA

	PATIENTS		
	TREATED	CONTROL	SPECIAL
Extension of infarction	1	3	2
Pulmonary embolus and new infarction		1	
Pulmonary and cerebral embolus	1		
Popliteal embolus	1		
Popliteal and cerebral embolus			1
Saddle embolus		1	
Thrombophlebitis		1	1
Cerebral embolus	1		
Total	4	6	4

DISCUSSION

The data in the two groups are comparable except for the higher incidence of angina in men of the treated series. The average age, sex distribution, pre-

existing hypertension, and the incidence of previous myocardial infarction are similar. The presence of hypertension, previous myocardial infarction, or the presence of angina did not significantly influence the mortality or the occurrence of thrombo-embolic phenomena in our series. The total mortality of 30.0 per cent is similar to the average figures reported. However, the incidence of thrombo-embolism is lower in both series than the average reported.

Our findings support the recent reports which question the value of anticoagulants in the routine treatment of acute myocardial infarction. Considering the fact that the use of anticoagulant drugs has certain disadvantages, such as daily venipuncture, cost, necessity of accurate prothrombin determination, and the hazard of serious bleeding,[17,18] the routine administration of these drugs in acute myocardial infarction is not favored by our data.

SUMMARY

1. One hundred eighty-nine cases of acute myocardial infarction werd studied to determine the value of anticoagulant therapy. These were dividee into seventy-six treated cases, seventy-six control cases, and thirty-seven in a special group.

2. The over-all mortality was the same in the treated and control groups (30 per cent) and very similar in the special group (24 per cent).

3. Thrombo-embolism occurred in four patients in the treated, six patients in the control series, and six patients in the special group.

4. Only minor bleeding episodes were encountered in four patients.

5. Our data do not favor the routine use of anticoagulant drugs in acute myocardial infarction.

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THE ACTION OF DICUMAROL IN THE HUMAN BEING ON PLASMA PROTHROMBIN TIME AND TOTAL PROTHROMBIN TIME

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SINCE Dicumarol is employed extensively, especially in the treatment of various types of heart disease, the one-stage prothrombin test which is practically indispensable for controlling the dosage of the drug has become of considerable clinical interest. It is becoming clear that if anticoagulant therapy is to be put on a sure footing, the prothrombin time test must not only become standardized but a satisfactory interpretation as to what the procedure measures must be found. The discovery of the labile factor in 1943[1] established that the prothrombin time is dependent not only on prothrombin but also on this new factor as well. It was shown, however, that the labile factor does not act as an accelerator and that any excess beyond the minimal required quantity has no further effect on the prothrombin time.[2] Dicumarol does not significantly affect the concentration of labile factor.[3] Therefore, it is unlikely that in estimating prothrombin by means of the one-stage test, changes in labile factor will be sufficient to introduce any appreciable error. In 1949 Quick and Stefanini[2] presented experimental findings which could be explained most satisfactorily by postulating that, in human blood, prothrombin exists partly in the active state and partly as a precursor. This concept as well as the conclusion that the one-stage prothrombin time measures only free or active prothrombin has been further supported by additional experimental findings.[4,5,6] With the development of a simple method to determine total prothrombin, it became feasible to study the action of Dicumarol on the concentration of the free and the inactive prothrombin in man, and thereby obtain additional information useful in evaluating and controlling this drug.

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EXPERIMENTAL DATA

The subjects selected for this study were patients who were given Dicumarol for heart disease. None had evidence of liver disease and, prior to treatment, had no evidence of a blood-clotting dysfunction.

Prothrombin Time.—The standardized procedure as originally described by the author was used. A prothrombin time of 12 seconds on normal plasma was invariably obtained.

Total Prothrombin Time.—When blood is carefully collected in silicone-coated glassware and centrifuged at a high rate, the resulting platelet-poor plasma when clotted yields a serum that has a much higher prothrombin activity than the plasma itself. In a previous publication[5] it was pointed out that this observation can best be explained by postulating that, during the clotting reaction, all of the inactive prothrombin is converted to free prothrombin. Since the lack of platelets prevents the conversion of prothrombin to thrombin, the prothrombin activity of the serum is the result of the free prothrombin of the plasma plus the quantity of prothrombinogen which becomes converted to active prothrombin. The prothrombin time of such a serum, therefore, is a measure of the total prothrombin. In a normal subject, the total prothrombin time is remarkably constant—eight to nine seconds.

The Procedure.—Blood is collected with a chilled silicone-coated syringe and needle and transferred to silicone-treated test tubes which are put in an ice bath. After ten minutes the blood is centrifuged in an Angle centrifuge for ten minutes at 8,000 r.p.m. The plasma obtained generally contains no more than 3,000 platelets per c.mm; 1 c.c. of plasma is put in a clean dry glass test tube which is put in a water bath at 37° C. As the fibrin is formed, it is removed with a glass stirring rod until coagulation is complete. The prothrombin in the serum is determined fifteen, thirty, and sixty minutes after clotting is complete. Almost invariably the clotting time becomes constant in fifteen minutes. The final value is taken as the total prothrombin time. The determination is as follows: 0.1 c.c. thromboplastin reagent, 0.1 c.c. 0.02M calcium chloride, and 0.1 c.c. fresh deprothrombinized oxalated rabbit plasma are mixed. Into this mixture, 0.1 c.c. of the serum is blown from a serologic pipette, and the time required for a clot to form is accurately timed. The test is carried out at 37° C. The detailed directions for preparing the reagents have been described.[7]

DISCUSSION

The effect of Dicumarol on the free and total prothrombin time is summarized in Fig. 1. It will be observed that as the prothrombin time of plasma increases, the total prothrombin time likewise becomes prolonged. It can be seen that there is a rough ratio of free to total prothrombin. Strikingly, however, the total prothrombin time may occasionally vary widely for any particular plasma prothrombin time.

While the one-stage method measures only free prothrombin, it is nevertheless a means to estimate approximately the total prothrombin because, as a pa-

tient is maintained on Dicumarol, a rough ratio of free to total prothrombin appears to become established. The routine prothrombin time is valuable in guarding against excessive reduction of prothrombin, because when the total prothrombin is markedly diminished, the free prothrombin also is low. Even Olwin,[8] who is critical of the one-stage method, recommended that it be employed to protect against hemorrhage. He states that ". . . it is a more accurate gauge of the likelihood of bleeding in a patient than is the two-stage test."

While the practical importance of inactive prothrombin (prothrombinogen) to hemostasis has not been determined, its theoretical significance cannot be disregarded. Whether it acts directly in hemostasis or whether it functions as a reserve for active prothrombin is difficult to establish experimentally. The

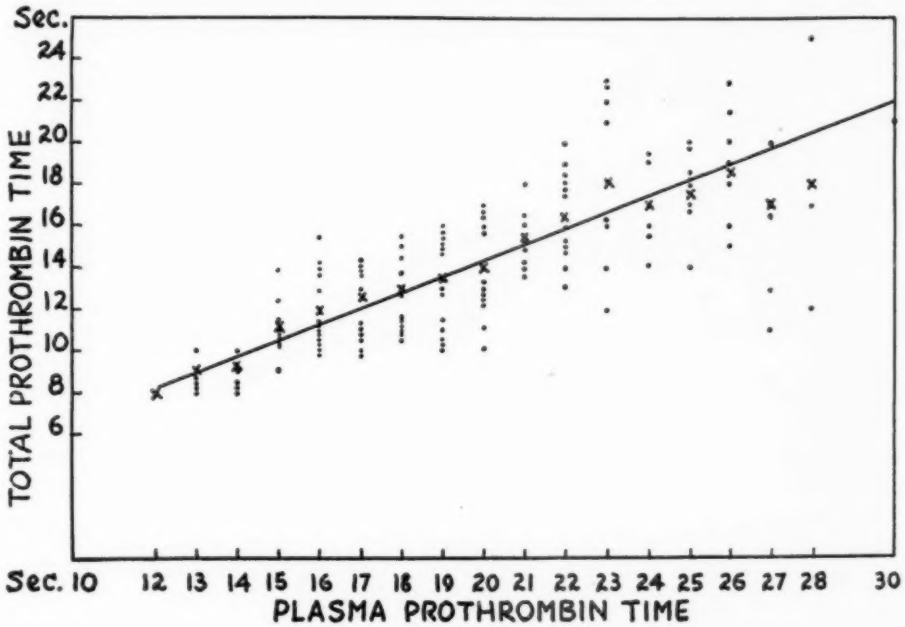

Fig. 1.—The relationship of the plasma prothrombin time to the total prothrombin time. Thirty-one patients were studied, and one hundred fifty-five determinations of free and total prothrombin were made.

observation of Quick and Favre-Gilly[9] that so little prothrombin is utilized in the complete clotting of blood in a test tube that it is difficult to estimate leads one to inquire how much prothrombin is actually consumed physiologically, that is, in in-vivo clotting. It is likely that too much stress has been put on the importance of the speed of prothrombin conversion. The fact that in certain hemophiliacs[10,11] a consistently normal clotting time is observed, even though they have an unmistakable bleeding tendency, makes it difficult to explain hemostatic dysfunction on delayed clotting per se, which is largely a measure of prothrombin conversion.

While the one-stage test has been and probably will remain, at least for the present, the mainstay for the control of Dicumarol therapy, the determination of

total prothrombin deserves to be studied further, both from the clinical and from the theoretical point of view. Hurn and associates,[12] Alexander and associates,[13] and Olwin,[14] who have studied the effect of Dicumarol both with the one-stage and the two-stage tests, have already supplied useful data. It seems fairly certain that the two-stage method estimates essentially total prothrombin because the various manipulations of the procedure undoubtedly cause the activation of nearly all of the precursor form. It is difficult, however, to correlate many of their results. Thus, Olwin[8] states that ". . . a plasma containing 5 per cent prothrombin by the two-stage test will usually register 15 to 30 per cent or more by the one-stage method." Quite the contrary is the observation of Hurn, Barker, and Mann.[12] They state, "With plasma of patients treated with Dicumarol, the Quick test always gives lower values than the two-stage procedure."

Obviously some gross difference in calculation or technique must account for such diametrically opposite results. Since the determinations in both laboratories were carried out by skilled technicians, it hardly seems possible that difficulties could have been encountered with the simple one-stage test. Very likely, the marked range of values observed with the two-stage method on normal plasma may explain, at least in part, the discrepancy in findings. Mann, Butt, and Hurn[15] reported that their normal plasma varied from 244 to 452 units per c.c. of plasma. In the one-stage test both the plasma and the total prothrombin times remain within exceedingly narrow limits. If the wide variations in normal subjects with the two-stage method were due to true fluctuations of prothrombin, one should expect that a similar range would be observable with the one-stage test. To postulate that accelerator factors compensate for decreases of prothrombin and thereby maintain prothrombin activity normal, as measured by the one-stage test, seems highly unlikely. In any study undertaken to compare the one-stage test with either the two-stage method or the new total prothrombin time procedure, much confusion can be avoided if exact values are obtained for normal blood or plasma. In reporting these values, the range as well as the average should be given, since this information is important for determining how well the analytical methods have been standardized.

While means are now available to determine the total prothrombin, there appears to be no need to employ such a test routinely for the control of Dicumarol therapy. The one-stage method when properly carried out insures the patient against excessive hypoprothrombinemia. It is being fairly generally accepted that the reduction of the prothrombin concentration to about 20 per cent (as measured by the one-stage test) furnishes the maximum therapeutic action with the minimum danger of hemorrhage.

SUMMARY

In man, Dicumarol causes an increase in the plasma and in the total prothrombin times. The explanation is offered that Dicumarol reduces both the free and total prothrombin and that a rough ratio between the two forms is maintained. The practical significance of this observation is discussed.

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INTRAVENOUS EMULSIFIED VITAMIN K_1 IN THE TREATMENT OF COUMARIN-INDUCED HYPOPROTHROMBINEMIA

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THE PROBLEM of combating severe hypoprothrombinemia associated with hemorrhage has plagued the physician.[1,2] It has been demonstrated repeatedly that the synthetic vitamin K products are relatively ineffective in reversing coumarin-induced hypoprothrombinemia.[3-10] This is particularly true in those patients who have been on the coumarin drugs up to the time of hemorrhage and in whom the circulating coumarin blood levels are still elevated. In contrast to this is the rapid reversal of hypoprothrombinemia with vitamins K_1 and K_1 oxide, even in the face of continued coumarin therapy.[6-17] Until recently it has been technically difficult to administer these products. They are quite photosensitive and have been difficult to prepare. The development of a stable emulsion for intravenous administration* has greatly simplified this problem.

It is difficult to state the absolute level of prothrombin depression at which bleeding may occur in an individual patient treated with the coumarin drugs. Bleeding at prothrombin levels of 30 to 40 per cent have been reported.[18] There is always the question of whether this might have occurred in the absence of anticoagulants or whether the measure of prothrombin may have been in error.

In our experience,[19] bleeding from coumarin therapy alone has not been encountered in patients with prothrombin levels above 10 per cent. The prothrombin level was determined by Ware and Stragnell's modification[20,21] of Owren's method,[22] using serially diluted, dried prothrombin standards for reference. Needless to say, this method has offered far more accurate and reproducible control of the effect of coumarin therapy. Despite this improvement in control, a number of instances of hemorrhage have been encountered that have appeared to be a primary result of coumarin therapy. In all instances hemorrhage occurred when the prothrombin was depressed below 10 per cent. In general this could be attributed to either excessive and ill-conceived dosage or to hyperreactivity of the patient to the drugs.

This report is concerned with the reversal of coumarin-induced hypoprothrombinemia in seven patients with emulsified vitamin K_1. In two instances the drug

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*Kindly supplied by Merck and Company, Inc., Rahway, N. J.

was given prophylactically where an overdose of coumarins had been administered but where no bleeding had occurred.

CASE REPORTS

CASE 1.—P. O., a 63-year-old white man with hypertensive and arteriosclerotic heart disease, was hospitalized with congestive heart failure. The patient was placed on prophylactic anticoagulant therapy with Tromexan.* In this case an excessive dose of Tromexan was given the afternoon of the fourth day and the following morning a prothrombin level of less than 10 per cent was recorded. At 11:00 A.M. the patient passed a tarry stool and the prothrombin level was found to be below 2 per cent. At 4:00 P.M. 300 mg. of emulsified vitamin K_1 were given intravenously. The following morning the patient's prothrombin level was 97 per cent. The patient's congestive heart failure had cleared and no further anticoagulants were given. No intrinsic cause of the gastrointestinal bleeding could be found and the patient was discharged. Fig. 1 summarizes the findings in this patient.

CASE 2.—A. P., an 82-year-old white woman with arteriosclerotic heart disease, was hospitalized because of congestive heart failure. The patient was placed on prophylactic anticoagulant therapy with Dicumarol. Slightly excessive doses of Dicumarol were given on the fourth, fifth, and sixth days and on the seventh day a prothrombin level of less than 10 per cent was recorded. At 5:30 P.M. on the fifth day the patient passed a tarry stool. At 8:00 P.M. she was given 200 mg. of emulsified vitamin K_1 intravenously. The next morning the prothrombin level had risen to 69 per cent, twelve hours after vitamin K_1 was given, and that afternoon the prothrombin was 110 per cent. Anticoagulants were not reinstituted. The patient expired during the night of the eighth day and no autopsy was obtained. The question of thrombosis, as a cause of death, could not be excluded. Fig. 2 summarizes the findings in this patient.

CASE 3.—O. G., an 85-year-old white man, was hospitalized with arteriosclerotic heart disease and congestive heart failure. Prophylactic anticoagulant therapy was considered. The initial prothrombin level of 45 per cent was ignored by the attending physician and 300 mg. of Dicumarol were given. The following morning a prothrombin level of less than 1 per cent was obtained and it was felt that prophylactic vitamin K_1 should be given. Seventy-five milligrams were given at 1:00 P.M., 7:00 P.M., and 12:00 midnight. The following morning the prothrombin level had risen to 75 per cent, and in the afternoon was 95 per cent. No further anticoagulants were given and no bleeding occurred. Fig. 3 summarizes the findings in this patient.

CASE 4.—F. L., a 53-year-old white woman with rheumatic heart disease, was hospitalized because of congestive heart failure. She was placed on prophylactic anticoagulant therapy and on the fourth day 50 mg. of Dicumarol were given despite a prothrombin level of less than 10 per cent. On the fifth day the prothrombin level was less than 10 per cent and at 7:00 P.M. the patient started bleeding from the nose. One hundred milligrams of emulsified vitamin K_1 were given intravenously at 9:00 P.M. The epistaxis ceased three hours after the vitamin K_1 was given. The following morning, eleven hours after the vitamin K_1 was given, the prothrombin level was 50 per cent and that afternoon was 89 per cent. Fig. 4 summarizes the findings in this patient.

CASE 5.—L. C., a 40-year-old white man with rheumatic heart disease and chronic congestive heart failure, had had a number of embolic phenomena and was maintained on ambulant anticoagulant therapy by an outside physician. The prothrombin level was checked by an unknown method at sporadic intervals and the patient was maintained on alternate doses of 50 and 100 mg. of Dicumarol. The day before entry the patient noted petechiae on his legs and the day of admission he had hematuria. On admission a prothrombin level of less than 1 per cent was found. The patient was given 100 mg. of emulsified vitamin K_1 intravenously and in fourteen hours the prothrombin level had risen to 35 per cent. The urine was free of red blood cells at this time. Subsequently, the prothrombin level rose to 112 per cent and large doses of Dicumarol were required to reinstitute hypoprothrombinemia. Fig. 5 summarizes the findings in this patient.

*Kindly supplied by Geigy Company, Inc., New York, N. Y.

CASE 6.—T. C., a 54-year-old white hypertensive man, was admitted to the hospital with congestive heart failure. Prophylactic anticoagulant therapy was considered but not recommended when an initial prothrombin level of 30 per cent was found. Tromexan was instituted despite this and the prothrombin level fell below 10 per cent. On the third and fourth days, although the prothrombin level was below 10 per cent, additional Tromexan was given. Although no bleeding was noted it was felt advisable to treat this patient with vitamin K_1. At 10:30 A.M. on the fourth day the prothrombin level was 4 per cent and 100 mg. of emulsified vitamin K_1 were given intravenously. At 12:00 noon the prothrombin level was 7 per cent, at 2:00 P.M. 10 per cent, and at 6:00 P.M. 21 per cent. The following morning the level was 46 per cent and that afternoon 73 per cent. Tromexan was reinstituted at this point and the patient responded

Fig. 1.

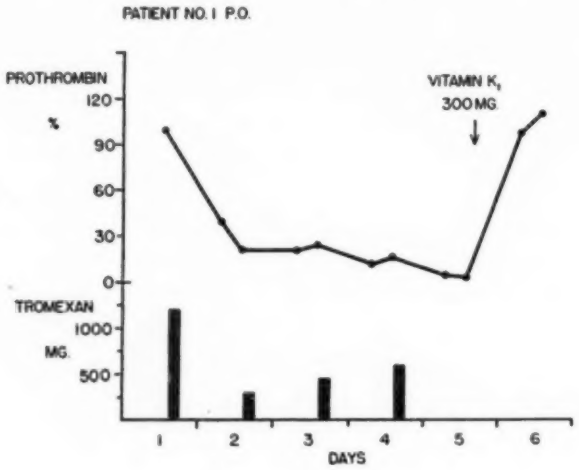

Fig. 2.

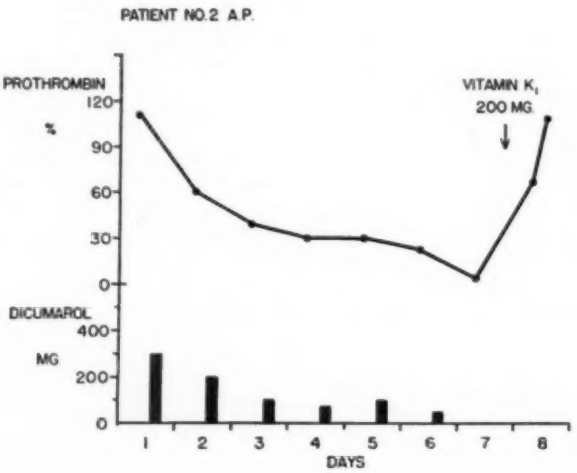

Fig. 1. (Case 1).—Patient P. O., who was given an excessive dose of Tromexan on the fourth day with low prothrombin level. On the fifth day a gastrointestinal hemorrhage occurred with a prothrombin level of less than 2 per cent. The prothrombin rose to 97 per cent sixteen hours after 300 mg. of emulsified vitamin K_1 was given intravenously.

Fig. 2. (Case 2).—Patient A. P., who on seventh day had a prothrombin level of less than 10 per cent; gastrointestinal hemorrhage occurred. There was prompt response to normal prothrombin level after vitamin K_1 was given. A prothrombin level was not obtained immediately prior to the administration of vitamin K_1 and the slope of rise of prothrombin level should be steeper than depicted.

moderately to this medication. Larger doses than would have seemed indicated, when his initial prothrombin level was considered, were needed. Fig. 6 summarizes the findings in this patient.

CASE 7.—A. B., a 70-year-old white man, was admitted to the hospital because of an acute myocardial infarct. The initial prothrombin level was 100 per cent. After a dose of 300 mg. of Dicumarol the prothrombin fell to 11 per cent on the second day and on the third day the prothrombin level was 2 per cent, and rectal bleeding occurred. One hundred milligrams of emulsified vitamin K_1 were given intravenously at 4:00 P.M. on the third day. The following morning, sixteen hours after the K_1 was given, the prothrombin was 64 per cent. Subsequently large

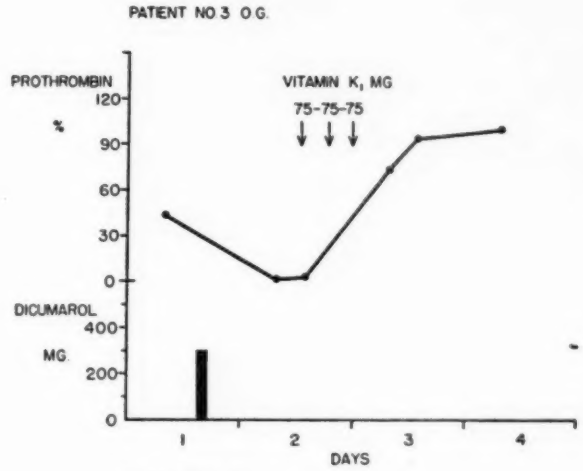

Fig. 3.

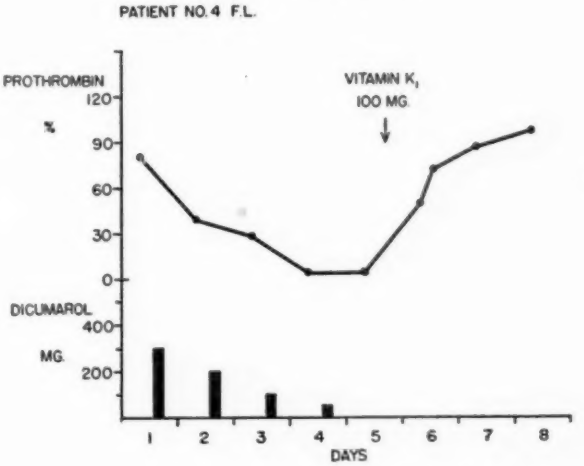

Fig. 4.

Fig. 3. (Case 3).—Patient O. G., in whom an initial level of 45 per cent prothrombin was found; however, inadvertently, 300 mg. of Dicumarol were given. The prothrombin level fell to less than 1 per cent, but promptly returned to normal following three intravenous doses of 75 mg. of emulsified vitamin K_1 at six-hour intervals.

Fig. 4. (Case 4).—Patient F. L., in whom coumarins were administered on the fourth day despite a prothrombin level of less than 10 per cent. Epistaxis occurred at 7:00 P.M. on the fifth day. At 9:00 P.M. 100 mg. of emulsified vitamin K_1 were given. In three hours the epistaxis ceased. The following morning the prothrombin level was 50 per cent. A prothrombin level was not obtained immediately prior to the administration of vitamin K_1 and the slope of rise of prothrombin level should be steeper than depicted.

doses of Dicumarol did not depress the prothrombin level and on the seventh day the patient developed severe precordial pain and shock, and expired. At autopsy, extension of the coronary occlusion and myocardial infarct was demonstrated. Fig. 7 summarizes the findings in this patient.

Fig. 5.

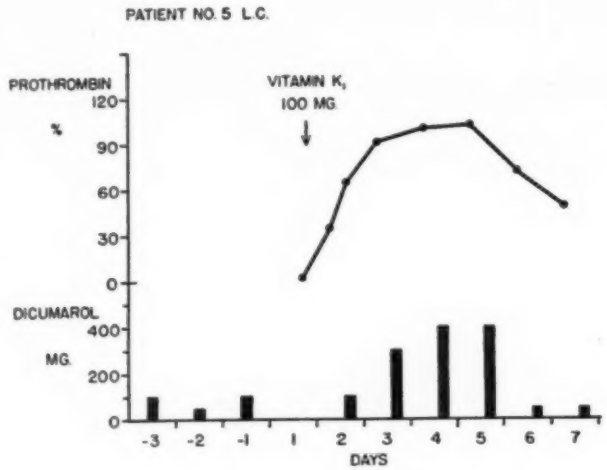

Fig. 6.

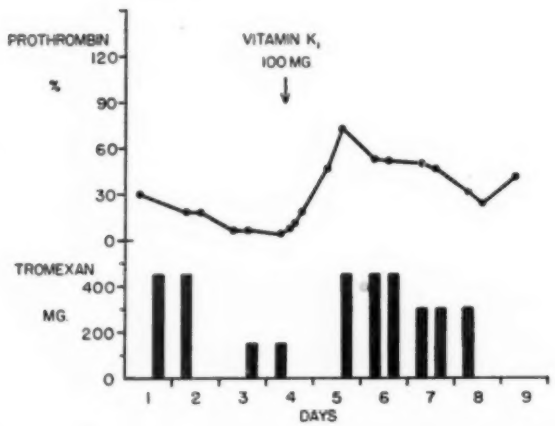

Fig. 5. (Case 5).—Patient L. C. had been maintained on ambulant anticoagulant therapy with poor control. He was admitted with gross hematuria and prothrombin level of less than 1 per cent. Fourteen hours after 100 mg. of emulsified vitamin K_1, hematuria had ceased and the prothrombin level was 35 per cent. Despite large doses of Dicumarol the rise in prothrombin level could not be reversed for several days.

Fig. 6. (Case 6).—In patient T. C., Tromexan was administered despite initial low prothrombin level. Although no bleeding occurred it was deemed advisable to administer vitamin K_1. Over twenty-seven hours the prothrombin level rose from 4 per cent to 73 per cent. Subsequent Tromexan therapy indicated a greater resistance to this agent than had been present prior to vitamin K_1 therapy.

DISCUSSION

Emulsified vitamin K_1 has been found to be a most satisfactory agent for reversal of coumarin-induced hypoprothrombinemia. The drug is supplied in a stable, nontoxic emulsion suitable for administration intravenously without

dilution. A prompt reversal of hypoprothrombinemia has been observed in all patients treated with this agent. In two instances death occurred after reversal of the hypoprothrombinemia. In one, extension of a coronary occlusion and myocardial infarct was demonstrated. In the other, no necropsy was obtained. In all instances when coumarin therapy was reinstituted, following the administration of vitamin K_1, resistance to the reinduction of hypoprothrombinemia was observed. This presents a serious problem where continued anticoagulant therapy is desired. At the present time, we recommend the adminmistration of heparin with the coumarin drugs until therapeutic hypoprothrombinemia can be reinstituted.

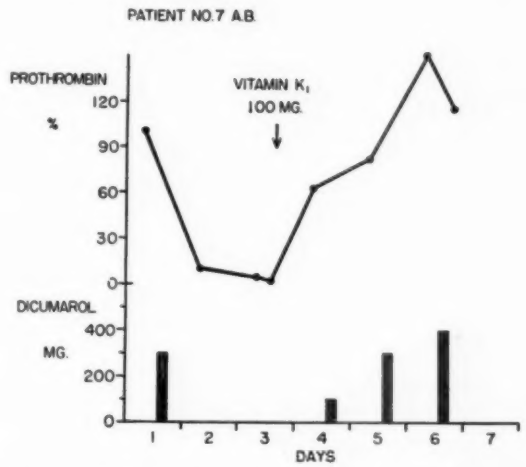

Fig. 7. (Case 7).—In patient A. B., Dicumarol was given in normal dosage. The patient was a hyperreactor to Dicumarol and rectal bleeding developed on the third day with a prothrombin level of 2 per cent. The prothrombin level rose promptly following 100 mg. of emulsified vitamin K_1 intravenously. Subsequently, the patient was very resistant to coumarin therapy. On the seventh day the patient died with an extension of the coronary occlusion and myocardial infarct.

We have found that as small a dose as 100 mg. of emulsified vitamin K_1, administered intravenously, is effective in reversing severe hypoprothrombinemia. This dose is effective even in cases that have been receiving coumarins up to the time of administration of the vitamin K_1. The response with this dose is not as rapid as has been described by other investigators with larger doses.[23] However, in our experience bleeding has ceased within three to four hours of the administration of this drug.

In none of the patients reported was bleeding sufficiently severe to require blood transfusion. At the present time it is felt that the administration of blood or plasma is indicated only to replace red cell loss and restore the circulating blood volume. It is true that some transient restitution of prothrombin may be accomplished by the administration of blood or plasma. In this regard it should be noted that prothrombin does not deteriorate materially on standing. We have found normal prothrombin levels in 6-year-old dried human plasma.[24] The admonition to administer *fresh* blood or plasma for replacement of prothrombin is unfounded.

SUMMARY

1. Seven patients with severe coumarin-induced hypoprothrombinemia have been studied. Rapid reversal of the hypoprothrombinemia has been obtained with as little as 100 mg. of emulsified vitamin K_1 administered intravenously.

2. Following the administration of vitamin K_1 the patients are resistant to coumarin therapy and a period of hypercoagulability appears to exist during this phase. This can be controlled by the administration of heparin with the coumarin drugs to safeguard the patient in whom the continuation of anticoagulant therapy is desired.

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THE EFFECT OF PITRESSIN INFUSION ON BLOOD PRESSURE OF THE RABBIT, CAT, AND RAT

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VANCOUVER, B. C.

THE CARDIOVASCULAR effects of pressor extracts of the posterior pituitary were extensively studied by routine kymographic techniques by many investigators prior to the present decade. Recently, we have been interested in the effects of pitressin in animals treated with desoxycorticosterone acetate (DCA). In these experiments, pitressin was given subcutaneously and presumably, therefore, was slowly absorbed over a relatively long period. It seemed important to know what effects had been noted by other workers on sustained infusion of the pressor principle. Surprisingly, a search of the literature yielded little information directly applicable to this point.[1] Accordingly, a reinvestigation of the pressor properties of pitressin was undertaken aimed at determining the effects of sustained infusion of the extract. This study was initiated using routine kymographic technique, but was repeated and extended using electromanometric methods with concurrent electrocardiographic recording. The effects were studied in the rabbit, cat, and rat.

METHODS

Anesthesia.—In the rabbit and cat, prolonged anesthesia was secured using urethane (20 per cent solution) and barbitone (barbital) (6 per cent solution). The anesthesia was kept light so that even the insertion of the cannula required supplemental ether inhalation or local Novocain infiltration. Nembutal (2.5 mg./100 Gm.) was used in the rat.

Blood Pressure Recording.—In the rabbit the initial experiments were undertaken using a standard tambour and smoked drum. Later experiments in the rabbit and all experiments in the cat and rat were carried out using the Sanborn electromanometer recording through a Twin-Viso Cardiette. Blood pressure was recorded from the femoral artery in the two larger species and from the aorta in the rat.

Injection.—In the rabbit, all infusions were carried out using the ear vein, in the cat using the femoral vein, and in the rat the jugular vein. Constant rate infusions were produced by a synchronous motor operating a constant-pitch screw device which actuated a syringe plunger. Variation in rate of infusion was produced by a second synchronous motor driving a variable cam device, which

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turned the first motor on and off for stated periods per minute. Simply stated, the device always delivered the same volume of fluid per operating second at the syringe tip. Variation in rate of infusion was produced by having the apparatus operate either continuously (sixty seconds per minute) or for as little as one second every minute.

Electrocardiograph.—In those cases where a synchronous electrocardiograph was obtained, Lead II was used, connections to the animal being secured by needle electrodes.

OBSERVATIONS

Effect of Single Intravenous Injection in the Rabbit.—Thirteen experiments were carried out using doses ranging from 0.02 units per kg. to 0.12 units per kg. The results obtained are summarized in Table I and agree with previously recorded observations of other authors.[1] The typical response occurring after a short latent period consisted of a sharp rise in blood pressure followed by a temporary fall (usually ascribed to coronary constriction), then a secondary rise in pressure to a peak level followed by a rapid fall back to normal.

Effect of Continuous Intravenous Infusion in the Rabbit.—Twenty rabbits were studied. The first eighteen were investigated using kymographic technique, the last two with the electromanometer. Doses administered ranged from 0.014 units to 0.33 units per minute per kg. while the duration of injection varied from eleven to sixty minutes. Table II presents the essential data.

TABLE I.

RABBIT WT. (Kg.)	DOSE (UNITS/Kg.)	LATENT PERIOD (SECONDS)	DURATION OF RISE (MINUTES)	MAX. RISE* (MINUTES)	MAX. RISE (mm. Hg)	DURATION OF FALL† (MINUTES)
2.5	0.02	15	5.5	2.5	45	3.5
2.5	0.02	15	12.0	2.5	55	9.0
2.7	0.02	10	?	1.0	40	7.0
2.7	0.04	20	7.0	5.0	55	3.5
2.5	0.04	30	18.0	3.0	40	15.0
2.5	0.06	30	35.0	2.5	55	30.0
2.7	0.07	15	8.0	2.0	45	6.5
2.7	0.07	15	12.0	3.0	35	10.0
2.4	0.12	15	9.0	4.5	45	5.0
2.4	0.12	20	4.0	2.5	35	3.0
2.5	0.12	45	8.0	5.0	50	3.0
2.5	0.12	45	7.0	4.5	40	2.5
2.6	0.12	10	13.0	4.0	50	11.0

*Maximum rise = time after injection of maximum rise.
†Duration of fall = time taken for blood pressure to return from maximum rise to base line.

Considering the kymographic studies first, it is apparent that, of the sixteen animals in which a satisfactory blood pressure rise was observed, only five sustained an observable (10 mm. Hg) rise for the full duration of infusion, while only eight sustained this rise for two-thirds or more of the injection period. In all instances where a rise was maintained, the continuing level was considerably below the peak. In general, as the two sample records in Fig. 1 show, there was

little difference between the effects of continuous infusion and those of a single injection, except that in the case of continuous infusion there was a small tendency for a minimal rise to be sustained for a more prolonged period. The coronary effect was absent at the lowest doses studied.

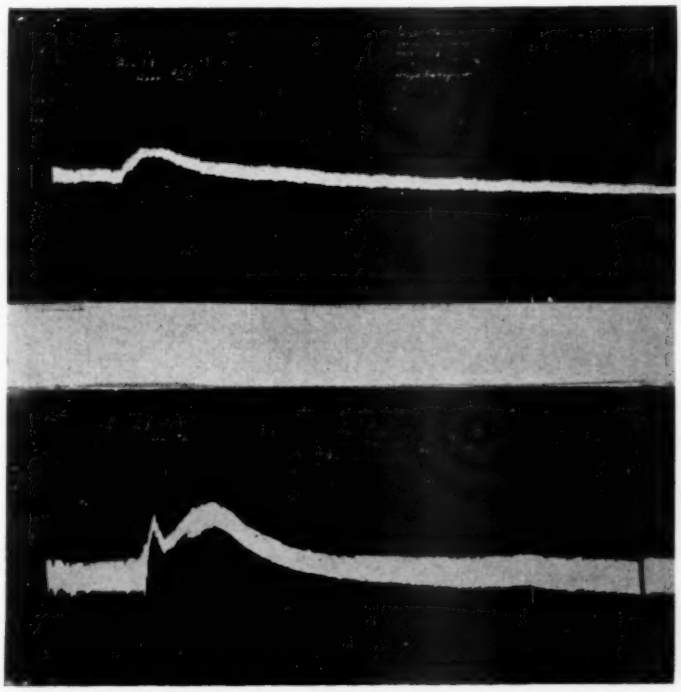

Fig. 1.

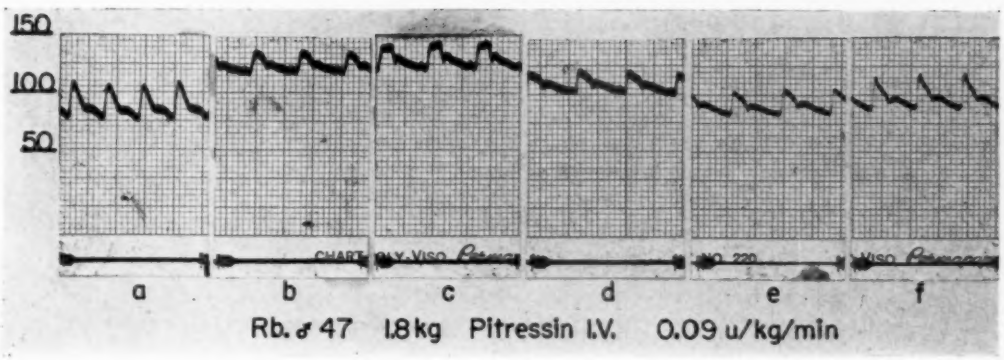

Fig. 2.

To amplify and confirm these observations, two rabbits were studied using the electromanometer and middle range doses were administered for sixty minutes. Lead II electrocardiographs were taken simultaneously. Fig. 2 presents sample records from one of these rabbits, while the actual data from these ani-

mals are plotted in Figs. 3*A* and 3*B*. Continuous electromanometric records substantiated the general conclusions derived from the kymograph. The initial steep rise in blood pressure fell off rapidly to be succeeded by a more moderate sustained elevation.

Pulse pressure remained remarkably steady throughout the infusion despite changes in both blood pressure and heart rate. The direct effect on the heart was only indicated by a minor and temporary fall in pulse pressure in one animal. Heart rate fell steeply during the period when the blood pressure was rising acutely and remained low throughout the infusion despite the varying hemodynamic

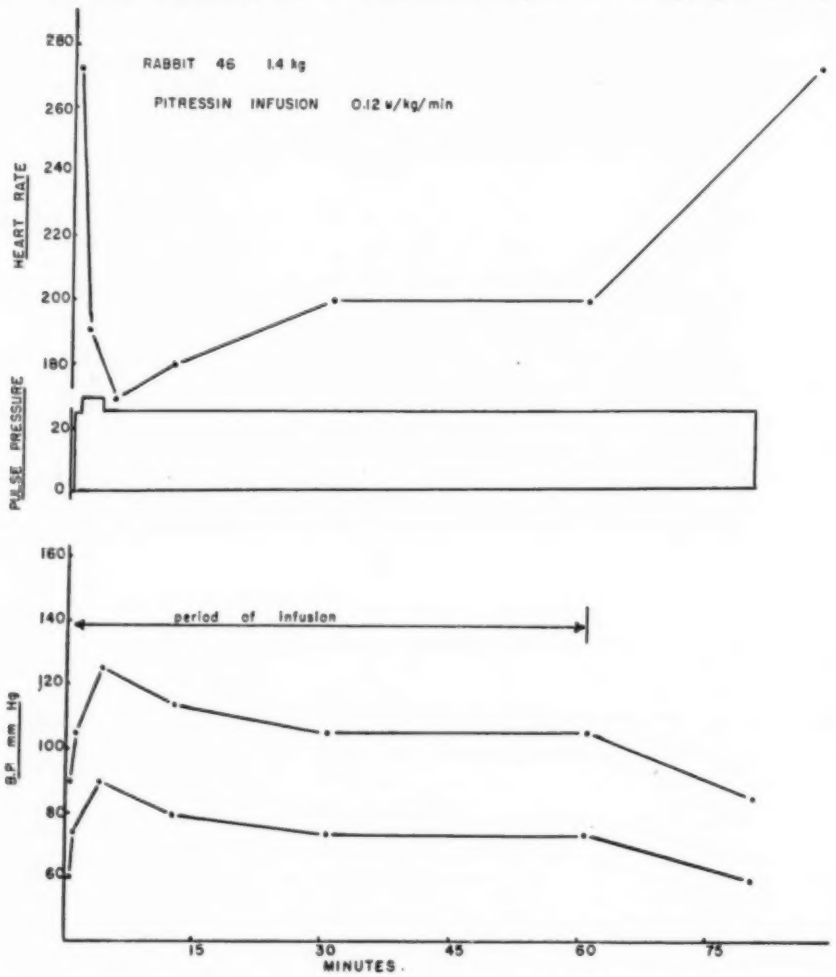

Fig. 3*A*.

picture. The suggestion is that pitressin, in addition to an initial coronary effect which is rapidly compensated, causes an over-all increase in peripheral resistance to which the heart responds by a slower and more forceful contraction. No significant electrocardiographic changes were observed with the exception of a moderate peaking of the T wave lasting about thirty seconds and occurring almost immediately after starting the infusion.

Effect of Increasing Intravenous Infusion in the Rabbit.—Seven rabbits were studied, the first four by kymograph, the last three with the electromanometer. The experiments were carried out in order to determine whether the initial marked elevation in blood pressure induced by pitressin could be sustained by increasing the dose at either regular intervals or when the blood pressure began its fall away from the peak. Table III outlines the procedures used. Fig. 4 shows two sample records which are typical of the kymographic observations, while in Fig. 5 the typical data obtained by electromanometer are plotted for one experiment.

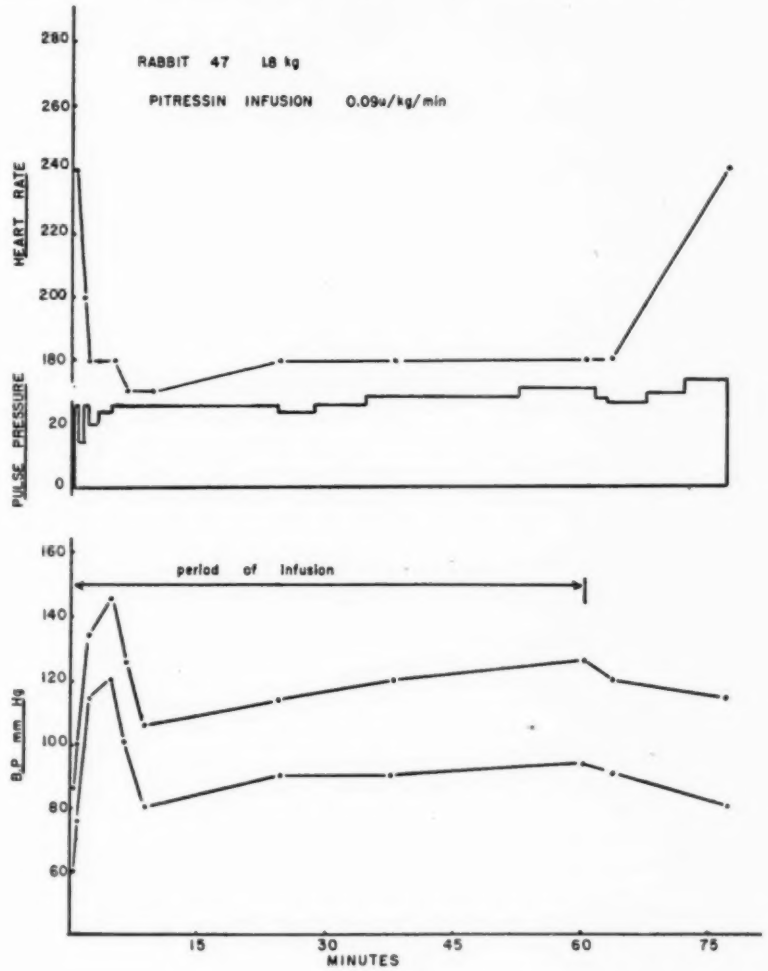

Fig. 3*B*.

The administration of increasing doses of pitressin tended, in general, to accentuate the resistance of the organism to the extract. The development of a marked resistance was demonstrated in rabbit 50 (Fig. 5) where ultimately the acute administration of 10 units of pitressin, followed by 10 more units one minute later, produced no effect whatever. The developing resistance was also

shown nicely by the pulse rate which, in contrast to the observations with continuous infusion, continued to return toward normal after the initial fall despite the increasing infusion of pitressin.

TABLE II

RABBIT NO.	WEIGHT (Kg.)	PITRESSIN DOSE (UNITS/ Kg./Min.)	DURATION OF INJECTION (MINUTES)	MAX RISE (mm. Hg)	DURATION OF RISE > 10 mm. Hg (MINUTES)	REMARKS
20	2.17	0.014	60	+40	60	
6	2.60	0.05	20	+40	12	
8	2.80	0.06	22	+45	22	
18	2.17	0.06	46	+25	30	
25	2.62	0.08	60	+30	15	
19	1.82	0.10	60	0	0	Marked coronary effect
29	1.82	0.10	60	+20	8	
15	3.18	0.11	20	+15	11	
14	2.84	0.12	21	+40	15	
15	3.18	0.15	14	Fall only	0	Marked coronary effect
11	2.84	0.17	15	+30	30	
12	2.70	0.17	15	+40	15	
21	1.82	0.18	60	+50	17	
26	2.62	0.19	60	+45	40	
9	2.60	0.20	11	+30	30	
17	2.05	0.21	18	+60	11	
22	2.05	0.30	42	+25	36	
21	1.93	0.33	48	+45	20	
46	1.40	0.12	60	+40	60	Electromanometer
47	1.80	0.09	60	+60	60	

TABLE III

RABBIT NO.	WEIGHT (Kg.)	DOSE SCHEDULE (UNITS/Kg./Min.)	DURATION OF INFUSION (MINUTES)	
26	2.28	0.004 increased by stages to max. of 0.07	41	Kymograph
27	2.40	0.04 increased by stages to max. of 0.33	30	
29	2.28	0.10 increased by stages to max. of 0.70	23	
25	2.73	0.10 increased by stages to max. of 0.60	22	
48	1.60	0.10 increased by stages to max. of 0.48	48	Electromanometer
49	1.60	0.10 increased by stages to max. of 0.40	40	
50	1.60	0.05 increased by stages to max. of 0.48 followed by rapid intravenous injection of 10 units in 21st minute and additional 10 units in 23rd minute	21	

Since we were primarily interested in extending these initial fundamental observations to a study of the mechanisms involved in the refractoriness to pitressin, two experiments were performed to determine whether this was a generalized hemodynamic reaction or a more specific resistance to pitressin itself. In the first, Adrenalin was infused for thirty minutes followed by pitressin; in the second, these infusions were reversed. In neither case did the one infusion affect the other. More importantly, despite the development of refractoriness to pitressin, Adrenalin still produced its expected pressure rise indicating the

specificity of the resistance to the pituitary extract. This resistance is now under further investigation.

The Effect of Continuous Intravenous Infusion in the Cat.—Two cats were studied using the electromanometer. The dose used, 0.1 units/kg., was one which had been in the middle of the range of doses used for the rabbit and had been well tolerated. Lead II electrocardiograms were taken together with blood pressure recordings.

Fig. 6 presents the data in graphic form. In contrast to the effect of continuous intravenous administration of pitressin in the rabbit, the cat responded with an elevation in pressure which tended to be well sustained throughout the period of infusion. A coronary effect was indicated by a temporary fall in pulse

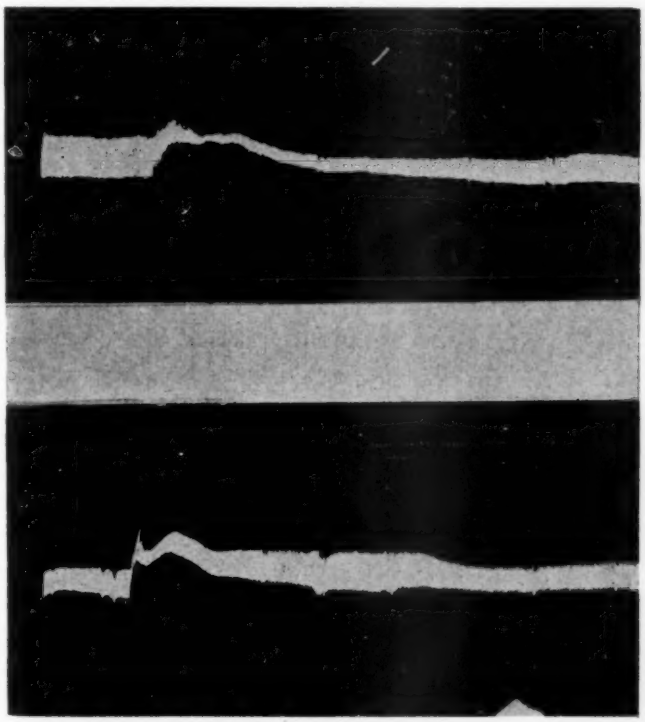

Fig. 4.

rate, and in one cat, by a temporary fall in pulse pressure. Pulse pressure in general remained remarkably constant despite fluctuations in blood pressure. Again, in contrast to the rabbit, heart rate remained rapid throughout the infusion. No electrocardiographic abnormality was noted and no change in pulse contour. Upon cessation of infusion a gradual return toward normal occurred.

The Effect of Continuous Infusion in the Rat.—Nine rats were studied at dose ranges beginning with the doses which had been well tolerated in the rabbit and cat and extending upward to very large doses at the limit of tolerance. Nembutal, 2.5 mg./100 Gm. was used as anesthetic and the aorta cannulated with a 20-gauge needle for electromanometric recording.

TABLE IV

RAT NO.	WEIGHT (Gm.)	PITRESSIN DOSE (UNITS/ Kg./Min.)	DURATION OF INFUSION (MINUTES)	INITIAL B. P.* (mm. Hg)	MAX. B. P. (mm. Hg)	INITIAL P. P.† (mm. Hg)	MAX. P. P. (mm. Hg)	B. P. AT CESSATION (mm. Hg)	B. P. AFTER CESSATION (mm. Hg)
1	240	0.07	6	108/80	175/125	28	50	175/125	170/125 5 minutes later
2	240	0.07	12	123/90	190/130	33	60	190/130	148/120 10 minutes later
3	240	0.07	13	108/63	163/130	45	33	163/130	110/75 10 minutes later
4	240	0.07	12	110/80	175/128	30	47	175/125	148/110 10 minutes later
5	250	0.14	9	120/78	200/140	42	60	200/140	Not obtained
6	250	0.21	12	98/73	178/123	25	55	178/123	148/118 10 minutes later
7	250	0.21	12	115/88	188/145	27	43	188/145	Not obtained
8	240	0.42	6	98/68	185/125	30	60	185/125	128/98 10 minutes later
9	240	0.80	6	100/75	190/130	25	60	190/130	138/108 10 minutes later

*B.P. = blood pressure.
†P.P. = pulse pressure.

The data are summarized in Table IV. In all instances pitressin caused a marked and immediate rise in blood pressure to a peak level which was reached within a minute or two and was sustained without indication of a fall for the whole period of infusion. The duration of infusion used in the rat was shorter than that used in the rabbit and cat but extended well beyond the time at which a fall had been observed in the former species. Not only was the blood pressure elevation

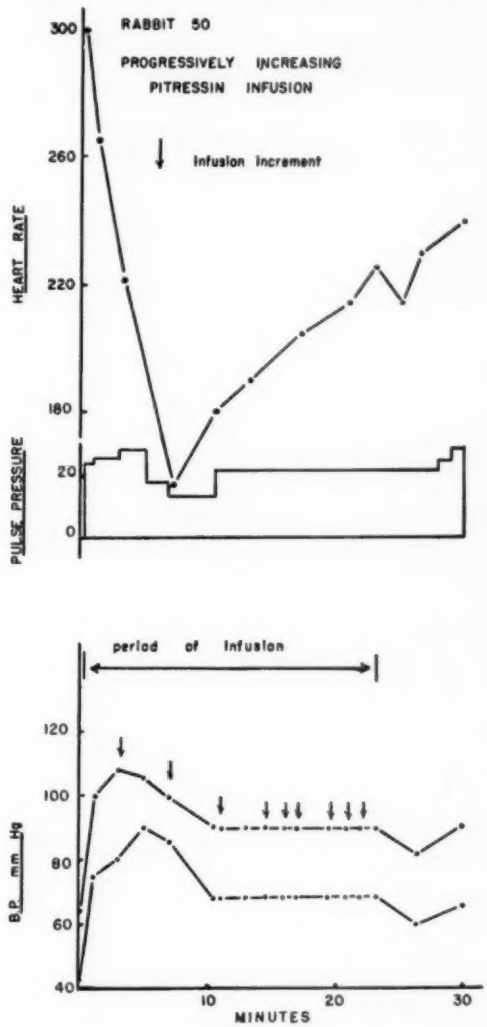

Fig. 5.

maintained throughout the infusion, but even after cessation the elevated blood pressure returned very slowly toward normal, in all observed instances still being well elevated after a lapse of time equal to the duration of the original infusion. At the height of the pressor response, pulse pressure was always increased (only one exception) while heart rate was inconstantly affected. No marked change in pulse pressure was observed. Fig. 7 shows the typical responses obtained.

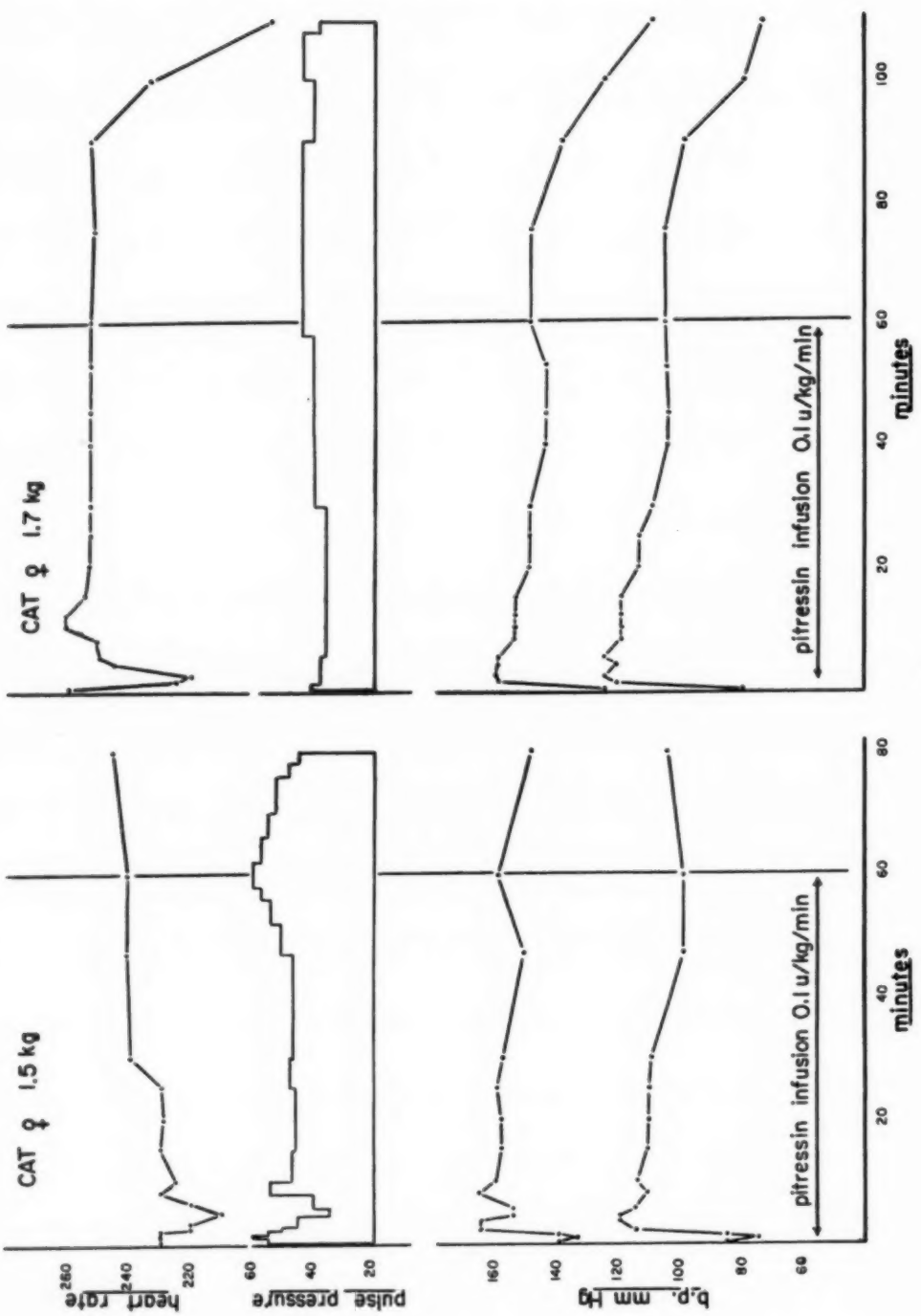
CAT ♀ 1.7 kg
CAT ♀ 1.5 kg
heart rate
pulse pressure
b.p. mm Hg
pitressin infusion 0.1 u/kg/min
minutes

Fig. 6.

The response in the rat was thus totally unlike that in the rabbit and much more similar to that observed in the cat. The major differences between the rat and cat were that the response in the rat seemed more dramatic, more sustained, and accompanied by a pulse pressure increase.

DISCUSSION

Although many pharmacologic studies of posterior pituitary extracts have been carried out, the mode of action and fate in the body of these extracts remain obscure. Most of the in vivo studies of the pressor principle have been concerned with the effects of single injections. Single intramuscular or subcutaneous injections of pitressin into an anesthetized rat produce a pressor response not obtained in the cat, rabbit, or man.[2] Single intravenous injections produce a transient pressor response in the rabbit and cat, a variable response in man, and a depressor response in birds.[1] Continuous intravenous infusion, similarly, in our experiments supports the idea of species variability, since it produces a transient pressor response in the rabbit (Fig. 1), presumably due to the development of tolerance, but a sustained pressor response in both the cat (Fig. 6) and the rat (Fig. 7). Interestingly enough in this connection, it has been noted that with successive

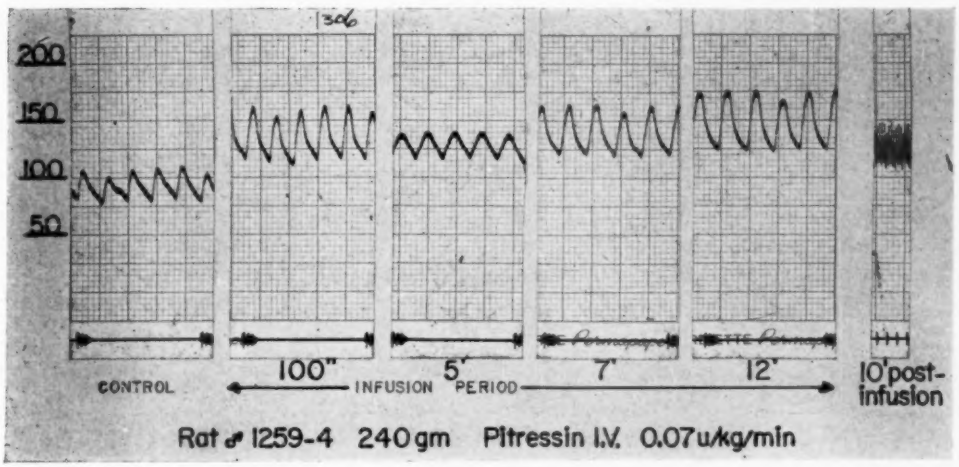

Fig. 7.

intravenous injections of pitressin a refractory state develops in the anesthetized rabbit and cat[2] but not in the anesthetized rat.[3] No explanation is offered at present as to why the cat responds like the rabbit to successive intravenous injections on the one hand, and more like the rat to continuous intravenous infusion on the other.

The development of refractoriness in the rabbit is not only rapid (Fig. 3) but also stable, since even massive doses fail to overcome it (Fig. 5). The sustained depression of heart rate during the infusion period suggests, however, that not all vascular tissues become equally refractory to the effects of pitressin. It should be noted, too, that in the cat, where the elevated blood pressure tends to persist, the heart is only temporarily slowed. It is possible that the difference in the

response of the cat and rabbit may at least partly reside in a different reaction of coronary vessels to the extract. Indeed, recent perfusion experiments have shown that with pitressin coronary constriction occurs in the rabbit while, in contrast, dilatation occurs in the cat.[4]

Little is known of the mechanism of tolerance. Even when cardiac factors are removed as with the Gibb's artificial heart, tolerance still occurs, suggesting its production in peripheral structures.[5] Various possibilities have been suggested in explanation.[6] For example, it has been suggested that pitressin may be excreted or destroyed. If refractoriness depends on this, however, the mechanism called into play must be extremely efficient since massive doses fail to overcome it. It has also been suggested that refractoriness may only be cardiovascular compensation. The rapidity with which the tolerant state develops would support this idea and studies using autonomic blocking agents are now in progress to determine the part played by autonomic reflexes in the response. Finally, it has been suggested that the organs responsible for the pressor effect may become insensitive. Infusion of Adrenalin in an animal refractory to pitressin, however, shows that the vascular system is still capable of responding to another pressor stimulus, suggesting a specific immunity, if any is present at all.

Certainly it would appear that investigations into the pressor actions of pitressin in animals and the normal role of this material in the intact animal leave much ground unexplored. In particular, the studies here reported, while providing some basic data regarding sustained infusions of pitressin, highlight the species specificity of the response.

SUMMARY

1. Continuous intravenous infusion of pitressin is followed by an immediate rise in blood pressure which is scarcely sustained in the rabbit, moderately sustained in the cat, and continuously sustained in the rat.

2. The failure of the rabbit to sustain a pressor response to a continuing infusion of pitressin appears related to the development of a marked refractory state, since even increasing the infusion to relatively massive amounts fails to prevent the return of the blood pressure toward normal levels.

3. No marked changes in pulse pressure were observed in the rabbit or the cat while the sustained hypertension observed in the rat was uniformly accompanied by an increase in pulse pressure.

4. Only transient irregularities in the electrocardiograph, a tendency to peaking of the T wave, were occasionally observed.

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UNUSUAL CYANOSIS IN A BOY WITH CONGENITAL PULMONARY STENOSIS AND TRICUSPID INSUFFICIENCY. FATAL OUTCOME AFTER ANGIOCARDIOGRAPHY

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WE HAVE recently had occasion to study a patient suffering from pulmonary stenosis with tricuspid insufficiency with cyanosis of a very unusual type. The autopsy revealed, moreover, the presence of a malignant carcinoid in the jejunum and extensive metastases in the liver. This combination of two rare conditions seems to us to be worthy of mention.

CASE REPORT

K.G. was a 19-year-old boy, weighing 49 kilograms (108 pounds), and whose height was 167 centimeters (65.1 inches). He had no pubes or axillary hair. There was no family history of cardiac or other malformations. Personal history was negative to the age of 6, when dyspnea on exertion was observed. There was no history of rheumatic fever. He was hospitalized with a diagnosis of bronchial asthma in 1943, 1945, and 1946. Hospital records from that time indicate the presence of sibilant rhonchi in connection with asthmatic attacks, the chief feature of which was, however, cyanosis and "exanthema" over the face and the body. Neither auscultation nor x-ray examination did at the time point to any cardiac disease; the liver was not palpable. A moderate eosinophilia was present. The cyanosis and the so-called exanthema seem to have increased until 1951 when liver enlargement and pitting edema were observed as well. At that time systolic and diastolic murmurs were heard over the heart. His general condition was impaired and the last three months prior to admission he had had difficulty in walking. The patient was referred to our hospital for further study.

The *physical examination* revealed a patient who was dyspneic even at rest and had moderate ankle edema. There was a reddish-blue cyanosis all over the body, most marked on the face and trunk, less so on the extremities. There was no clubbing of fingers or toes. On the dorsal side of the forearms there was a brownish, scaly thickening of the skin, which was suggestive of pellagra. When the patient felt nervous or excited, the cyanosis rapidly changed into a sharp, vermilion color, which appeared and disappeared in circular spots, large as coins, particularly on the chest and abdomen. These red spots were 0.5 to 1.2° C. warmer than the adjacent skin. The cyanosis was little, if at all, influenced by the breathing of 100 per cent oxygen. On close inspection the cyanosis seemed to be, at least partly, due to small dots of less than pinhead size and very much like petechiae. However, tests of capillary fragility proved negative.

Over the heart, which appeared to be somewhat enlarged, especially to the right, pulsations were felt along the left sternal border and a weak systolic thrill in the fourth left intercostal space. The rhythm was regular. There was a second-degree systolic murmur over the aortic area and a clear second sound. Over the pulmonary area the murmur was somewhat louder and there was a second sound, not duplicated, which was followed, after a pause, by a diastolic murmur. The same type of murmur, though with a stronger diastolic accentuation, was heard down to the place

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of the thrill. There was no accentuation of the first sound and no impression of a mitral stenosis, though, according to the phonocardiogram, the diastolic murmur was located in presystole. The murmurs were less loud in the axilla and to the right of the sternum. The blood pressure was 120/100 mm. Hg.

The liver was markedly enlarged and reached below the umbilical plane. It was nontender, soft, and vigorously pulsating. A second-degree systolic murmur was heard over the site of the liver. The spleen was not palpable.

Laboratory findings revealed a negative Wassermann test, hemoglobin 84 per cent, and red blood count 4.6 million. White blood count and differential count were normal; thrombocytes 210,000; hematocrit 36 per cent, and methemoglobin negative. The urine was albumin negative and sugar negative; urobilinogen and urobilin negative. Bilirubin was found to be 0.64 mg. per cent. Thymol and Takata tests were negative. Cholesterol was 97 mg. per cent. Total serum protein was 5.4 per cent, of which 2.6 per cent was globulin. Nonprotein nitrogen was 30 mg. per cent.

X-ray examination of the chest.—The heart was enlarged to the left but not to the right, possibly because of a right ventricular hypertrophy. The pulmonary conus was replaced by a concavity. The lung fields were normal. The picture was suggestive of pulmonary stenosis. X-ray examination of the abdomen showed a liver enlargement down to the iliac crest.

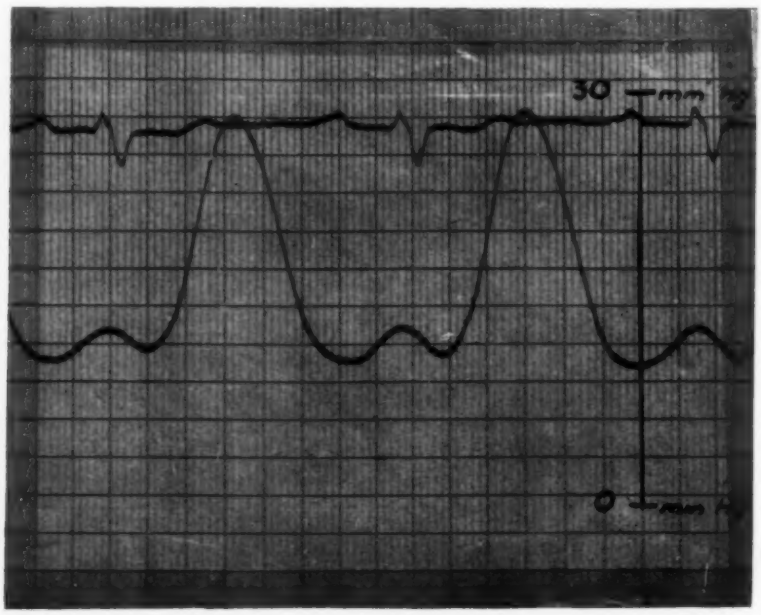

Fig. 1.—Pressure tracing from the inferior vena cava.

Electrocardiographic studies revealed a right bundle branch block. QRS potentials in right-sided chest leads were directed upward.

On cardiac catheterization (by Dr. H. Krook) the catheter could not be passed into the right ventricle because of the very high back pressure through the tricuspid valve. The pressure in the right auricle was 24 systolic—10 diastolic, with a mean pressure of 15 mm. Hg. Similar values were obtained in the superior and inferior venae cavae (28-12 mm. Hg). Arterial oxygen saturation was 90 per cent; right atrial blood and blood from both venae cavae showed 56 per cent saturation in several samples. The calculated cardiac output was 3.6 L.

Because of the peculiar type of cyanosis, an ophthalmiatric specialist (Dr. Österlind) was consulted. The refraction was normal. The color of the papilla changed spontaneously from pink to brownish violet. Pressure upon the ocular bulb very easily induced venous collapse and resulted in a pinkish color. These color changes were ascribed to a change in the degree of capillary filling and of the oxygen saturation of capillary blood.

The expansile liver pulse was undoubtedly a sign of tricuspid insufficiency. In view of the findings at x-ray examination and cardiac catheterization the tricuspid insufficiency was suspected to be secondary to some malformation of the pulmonary artery which might be amenable to surgical interference. Angiocardiography was therefore performed with 50 c.c. of 70 per cent Umbradil, after previous ocular and intravenous tests for iodine hypersensitivity, which were normal. The angiocardiography was performed through a cardiac catheter in the right auricle in order to obtain as good opacity as possible in consideration of the regurgitation of blood from the tricuspid lesion. On the angiocardiograms the catheter was seen to be nicely placed in the middle of the right auricle. Pentothal Sodium anesthesia with oxygen hyperventilation was used without any apparent discomfort. Ten minutes following the x-ray exposure and the termination of anesthesia induction, when the patient was beginning to wake up, without previous warning, the liver pulsation suddenly ceased and a cyanosis appeared which now was visible also on the ears and the nose. The pulse disappeared and the electrocardiogram showed slow contractions of a very broad bundle branch block type. Artificial respiration after intubation was immediately carried out, together with beating against the left lower chest. Adrenalin was given first intramuscularly, then intracardially. Despite all measures undertaken for more than one hour, the patient did not recover.

The *angiocardiograms* showed a great dilatation of the right atrium, which formed the entire right cardiac silhouette and was bulging posteriorly into the right ventricle. The right ventricle likewise was grossly enlarged. These two chambers filled slowly with contrast to an equal extent. The superior vena cava was filled with contrast retrogradely. At the site of the pulmonary valves there was a circular narrowing occupying about 1 cm. of the vessel. The pulmonary conus appeared rather tiny. The pulmonary arteries were of normal size. The contrast remained within the right side of the heart for at least ten seconds and during this time there was no filling of the left side of the heart or the aorta. A diagnosis of valvular pulmonary stenosis and tricuspid insufficiency was made.

The *autopsy* (by Dr. S. Winblad) revealed several interesting features. First, there was a pink spotted color all over the body and the livores were pink as in carbon monoxide poisoning. There were no definite signs of edema of the brain or meninges, nor was there any pulmonary edema.

The heart was enlarged. The right ventricle exceeded the left one in size, and the wall was more than one-half as thick as the left ventricular wall. The apex cordis was made up by the right ventricle. There were no septal defects. The pulmonary artery showed a moderate stenosis, permitting the entrance of a little finger but not of a middle finger. The stenosis was felt as a firm, narrow, tight ring consisting of the poorly separated pulmonary valves. The edges of the latter were thickened, but there were no signs of endocarditis. The tricuspid orifice was very wide. The valves were thickened and the chordae tendineae short and thick with no macroscopic signs of endocarditis. The right atrium was markedly enlarged with hypertrophy of the musculature.

In the middle of the small intestine there was a small tumor with one single glandular metastasis. The very large liver was entirely filled with large, yellow metastases from the tumor.

The *microscopic* examination showed in the *skin* an extreme dilatation of all capillaries and postcapillary venulae.

The *tumor* was found to be a malignant carcinoid growth.

There was a general fibrosis and an acute infiltration of round cells in the tricuspid valves. The pulmonary valves showed a capillary infiltration but no signs of acute inflammation. There was also slight fibrosis of the minor pulmonary vessels, but otherwise no pathologic findings.

The diagnosis of pulmonary stenosis with tricuspid insufficiency was thus verified. In addition a malignant tumor with liver metastases was found. The immediate cause of death could not be established.

DISCUSSION

Recent studies carried out all over the world have indicated that isolated pulmonary stenosis is more common than previously believed.[1-6] To our knowl-

edge, however, no case with the combination of pulmonary stenosis and tricuspid insufficiency has been reported, although a functional tricuspid insufficiency might be expected in cases with marked stenosis and high pressures in the right ventricle, inducing hypertrophy and dilatation. The pulmonary orifice of our patient was not particularly narrow when compared with those seen in many other cases. It is, therefore, not likely that the pressure in the right ventricle necessarily should induce a tricuspid valve lesion. The anatomic and histologic findings indicate an endocarditic involvement of the tricuspid valvular lesion. Whether the latter was of congenital origin cannot be determined. The pulmonary stenosis apparently was congenital.

The most interesting feature was the type of cyanosis. Cyanosis which is more marked on trunk and face (with the exception of nose and ears) than on hands and feet is rather uncommon. The absence of clubbing may indicate that the more intense cyanosis was of so recent a date that clubbing had not had time to develop.[7-9] The patient's blood counts showed slight anemia instead of polycythemia, despite the somewhat low arterial oxygen saturation of 90 per cent. However, the oxygen utilization was not exceedingly high as venous blood from the right auricle and the venae cavae contained 56 per cent oxygen. Why, then, was the patient cyanotic? It is our impression that the cyanosis was due to the visualization of the grossly dilated capillaries and postcapillary vessels, and to the slow passage (or even regurgitation?) of the blood through these vessels because of the markedly elevated right auricular pressure. Only on certain occasions, as on excitement, did the skin color become normal, or even more reddish than normal, almost as in histamine-induced hyperemia. This may have been due to the combined effect of increased arterial blood pressure and decreased peripheral resistance,[10] such as is usually seen in anxiety states, together with a marked dilatation of the subcapillary venous plexus,[11] facilitating a more distinct change of color. Ordinary pressure levels in arterioles and capillaries do not much exceed the central venous pressures recorded here on cardiac catheterization. Perhaps even a minute increase in arteriolar pressure caused a marked change in the dynamics of the capillary and postcapillary vascular bed.

Carnegie[12] has recently drawn attention to the dangers of angiocardiography, particularly in cyanotic heart disease. These dangers may be connected with hypersensitivity to the injected iodine, with an effect of the iodine on cardiac or cerebral cellular metabolism or with the anesthesia itself. In view of the very few instances of hypersensitivity reaction observed in other roentgenologic studies with iodine injections (pyelography), the former explanation is unlikely. It should not be forgotten, however, that hypersensitivity reactions may be masked during anesthesia, only to appear when the anesthesia effects disappear. This explanation is possible in our case. Disturbances of cardiac action[13] and on cerebral activity[14] have been reported following angiocardiography. In the first instance a direct connection with the injection is obvious. In the latter case, however, it may be difficult to ascertain whether the disturbances observed are due to the anesthesia, the injected iodine, or both. The advice given by Carnegie seems worthy of consideration, namely, to avoid anoxia during anesthesia as far

as possible by the administration of cyclopropane, ether, and oxygen through an endotracheal tube. The same applies to his recommendation of oxygen administration also after the termination of the anesthesia.

Finally, the occurrence in this boy of another very rare disease,[15-17] namely, a malignant carcinoid of the jejunum with metastases to the liver, likewise deserves consideration. The question of a causal relationship on a congenital basis or a plain coincidence presents itself. In view of the usually very slow growth both of the tumor itself and of its metastases, the former possibility cannot be excluded. It is, furthermore, remarkable that despite all these liver metastases and the presence of a high pressure in the hepatic veins, the interference with the liver function as judged from the simple liver tests was limited to low cholesterol and protein values and perhaps also the anemia.

SUMMARY

A case of congenital pulmonary stenosis with tricuspid insufficiency and a peculiar type of cyanosis in an 19-year-old boy is described. The patient died in connection with angiocardiography. At autopsy, the clinical diagnosis was verified; in addition to the cardiac lesion there was a malignant carcinoid of the jejunum with metastases to the liver. The findings are briefly discussed and an explanation of the type of cyanosis is suggested.

ADDENDUM

Recently, an autopsy was performed at our hospital on a 64-year-old man who had valvular stenosis of the pulmonary artery and malignant carcinoid of the ileum with metastases to various abdominal organs. There had been some cyanosis of the face but no vascular phenomena of the type mentioned in the article. Another patient with an intestinal carcinoid, a middle-aged woman, was recently seen by Prof. J. Waldenström and Dr. E. Ljungberg. There was no evidence of heart disease but peripheral vasomotor symptoms of a type similar to the one described above were displayed. Such vermillion spots are sometimes observed in patients with Raynaud's disease.

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Clinical Reports

ELECTROCARDIOGRAM PATTERN IN STAB WOUND OF THE HEART: CASE REPORT

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THE DRAMATIC nature of the successful surgical repair of a stab wound of the heart, combined with an electrocardiographic study during a comparatively long follow-up period, makes it worth while to add this case report to the relatively small, albeit gradually increasing, number of cases that have been investigated. The first attempt at surgical repair was made in 1882 by Block but it did not succeed. It was not until 1896 that the first successful treatment was reported by Rehn (quoted by Beck[2]). Since then, improvements in technique, anesthesia, etc., have made it possible for more and more of these cases to be treated successfully.

Electrocardiograms in such cases were described first in 1924[5,9] but only few were done prior to the 1930's. Even up to 1946 there were only slightly more than 100 cases in which electrocardiograms were recorded.[7] The earlier cases were not studied with any type of chest lead since the use of chest leads had not yet been introduced. Of those cases reported, not many were kept under observation for any significant length of time. Naturally, there have been more reports since 1946,[1,4,6,8] but their number is not great.

While we are not primarily concerned here with diagnosis or treatment, it might, nevertheless, be mentioned that treatment is generally considered to be a surgical emergency. Diagnosis is obviously very important. The patient usually presents a fairly characteristic picture which includes most of the following points: (1) history of chest wound, (2) a variable "symptom-free" period during which surprisingly "normal" activity may be tolerated prior to collapse, (3) circulatory collapse beyond that due to obvious external blood loss, (4) faint, distant-sounding heart tones, (5) weak or absent peripheral pulsation, (6) low blood pressure, (7) increased venous pressure, even up to 200 to 300 mm. water, (8) marked dyspnea, (9) pallor and/or cyanosis, and (10) eventual coma. The failure to detect cardiac pulsation fluoroscopically, with or without the char-

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acteristic "water-bottle" configuration, is tentative evidence of a cardiac wound with actual or impending tamponade. Beck's triad[3] of symptoms of acute cardiac compression includes (1) a falling arterial blood pressure, (2) a rising venous pressure, and (3) a small quiet heart.

CASE REPORT

T. M., a 19-year-old youth, was admitted to the Emergency Service of the Douglas County Hospital on April 24, 1949, at 10:50 A.M. because of severe chest pain and dyspnea, and stab wound of the chest. The patient had been stabbed in the chest during a fight about thirty minutes before admission and had run two blocks before collapsing. Family history and past medical history were noncontributory. There was no external bleeding, but the skin was pale. A laceration about 2 cm. in length was noted in the fifth intercostal space in the left midclavicular line. Routine chest examination was recorded as being within normal limits except for diminished breath sounds in the left base. Respiratory rate was 30 per minute; heart rate was 140 per minute. Heart sounds did not seem to be diminished in intensity and there were no murmurs. Arterial blood pressure was unobtainable. Venous blood pressure was 132 mm. of water. X-ray examination of the chest made with a portable unit showed a "bottle-shaped heart" and an increased density in the left lung field, presumably caused by the presence of fluid.

Diagnosis of stab wound of the heart was made and operation was performed by Dr. J. D. Bisgard. Since specific description of the wound as observed at operation would be pertinent in relation to electrocardiographic interpretation, we quote from the operative record: "There was a three centimeter laceration in the left ventricle, on the anterior surface, near the apex. This produced extensive bleeding with each systole. There was no evidence of fibrillation during the entire procedure." Further details of the operation, however, or of the postoperative course need not be discussed here. Suffice it to say that recovery was uneventful and the patient was discharged as ambulatory on May 21, 1949. He has been seen subsequently at various intervals for a period of nine and one-half months and has showed neither objective nor subjective evidence of impaired cardiac function. Electrocardiographic studies were started two hours after the operation. Unfortunately, the equipment was not available in time to make a preoperative record. A total of fifteen recordings, first at short and then at gradually increasing intervals, as indicated in part in the accompanying illustration (Fig. 1), were made.

COMMENTS

As seen in the first tracings, the elevation of the RS-T segment, most pronounced in Leads I, II, CF_5, and CF_6, but also present in CF_2, CF_3, and CF_4, reached a maximum in about three or four days and then began to subside toward the end of the first week. This elevation was only slight in some of the leads at the beginning of the second week, and the segment had returned essentially to isoelectric level by the end of the second week.

The T waves increased in amplitude in all leads in the first twenty-four hours and then began to round off. Their potential dropped progressively, the extent and rate of fall varying with the leads studied, and actually had a negative value in some of the leads by the end of the first week. By the end of the second week they began to return to a positive value in Lead III, but remained negative in Leads I, II, and in the precordial leads, except CF_1, where they had been negative and now became positive. After the second week the T waves became positive in all limb leads but remained negative in the CF leads, except CF_2, where they became positive in the last two tracings, and CF_6, where they were positive in the last tracing taken nine and one-half months after the injury.

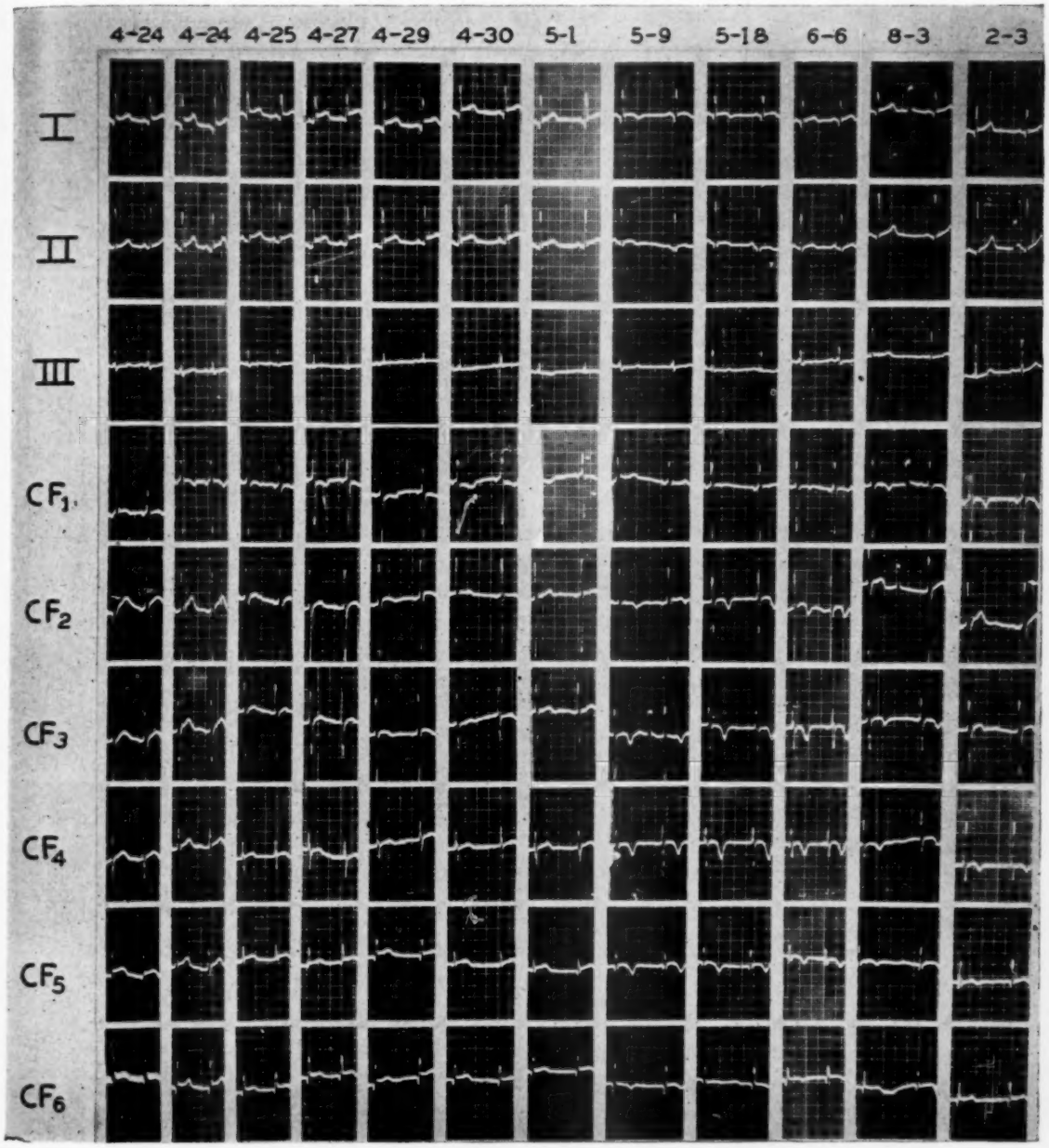

Fig. 1.—Twelve of the fifteen electrocardiographic records made in the reported case. The first one was made 4/24/49 at 4 P.M., two hours after surgical repair and/or about five hours after admission. The second one was made on the same day, but seven hours after the first tracing; the third one on the following day, twelve hours after the second tracing. The others were made on the dates indicated, the last one on 2/3/50, about nine and one-half months after the date of the infliction of the stab wound. For description of electrocardiographic changes, see Comments in text.

The QRS complexes showed variations in amplitude which in some cases remained for a long time and did not seem to return to normal even nine and one-half months after the first recording. A prominent Q wave was seen in Leads I, II, CF_5, and CF_6. It persisted in Leads I, CF_5, and CF_6.

No noteworthy changes were found in the P wave.

In other words, this series of electrocardiograms shows, first, the T-type of pattern associated with a pericarditis, although there were also Q-wave changes during the first few hours. The Q-wave changes then disappeared but returned later together with the other evidence of myocardial damage, the T-wave inversions, and the RS-T segment bowing. In connection with the latter, one must bear in mind the possibility that such changes could be related to shock, anemia, operative trauma, as well as to the myocardial injury itself. They, therefore, cannot be considered definitely significant diagnostically. Such changes as do persist even up to almost ten months after the trauma probably represent permanent electrocardiographic evidence of the cardiac injury. The electrocardiographic changes illustrated here agree essentially with those presented by others.

Solovay[9] states that "Electrocardiographic alterations of the first week or ten days following suture of heart wound are due to pericardial inflammation, as indicated by elevation of the RS-T segment in the first two leads or in all three and most marked in lead 2. The first Q waves usually do not give much of a clue. The T-wave inversion found later represents the late evidence of destruction of localized area of myocardium caused by the original trauma, subsequent suturing and, if a coronary vessel was ligated, infarction."

Noth[7] also commented that "Early changes are due to the practically universal presence of pericarditis, unless there is laceration or ligation of a coronary vessel. Under such circumstances one may have localizing RS-T and T-wave patterns during first twenty-four hours. These are later obscured by the pericarditis changes."

SUMMARY

An electrocardiographic study following successful surgical repair of a stab wound of the heart and extending over a period of about ten months is reported.

We wish to acknowledge the kindness of Dr. J. D. Bisgard, Department of Surgery, College of Medicine, University of Nebraska, in permitting use of this case for the studies carried out.

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EFFECT OF PROCAINE AMIDE ON ANOMALOUS CONDUCTION AND PAROXYSMAL TACHYCARDIA IN A CASE RESEMBLING THE WOLFF-PARKINSON-WHITE SYNDROME

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THE USE of oral procaine amide (Pronestyl) was followed by return of a paroxysmal nodal tachycardia to normal sinus rhythm. The history in this patient of many prior episodes of tachycardia together with unusual electrocardiographic findings made the case one of interest.

CASE REPORT

A 35-year-old white soldier was admitted to the 11th Evacuation Hospital on Nov. 5, 1951, because of rapid and forceful heart action of four hours' duration.

He had experienced repeated episodes of tachycardia, beginning two and one-half years before admission. Each attack began suddenly, with the sensation of the heart's "turning over." The rhythm during a paroxysm always seemed regular. The duration was ten to fifteen minutes, with abrupt, spontaneous cessation. The attacks were accompanied by dyspnea, dull substernal burning, aching pain in both upper extremities, and dizziness. He could not correlate the occurrence of paroxysms with exercise, fatigue, food, tobacco, or alcohol. Although there had been about forty previous attacks, the presenting paroxysm was the longest the patient had experienced.

Physical examination disclosed a robust young man who took occasional deep, sighing respirations. The pertinent findings were limited to the cardiovascular system. The blood pressure was 90/76. The ventricular rate was 180 per minute and regular. No murmurs were heard. No change in cardiac rate or rhythm followed right, left, or bilateral carotid sinus pressure or deep ocular pressure. A chest roentgenogram, routine hematology, and urinalysis were all within normal limits. The electrocardiogram on admission (Fig. 1) revealed a nodal tachycardia of 188 beats per minute. Retrograde P waves were visible in Lead I.

After six hours of sustained tachycardia, the patient was given 1 Gm. of procaine amide by mouth. Twenty minutes later he noted the sudden return of normal rate.

The electrocardiogram (Fig. 2*A*) then revealed a sinus rhythm with ventricular rate of 84 per minute, P-R interval of 0.16 second, and QRS complexes of 0.08 second duration. The QRS deflections were of similar configuration to those recorded during the paroxysm. Because of the history of recurrent episodes of tachycardia, repeated tracings were taken in an attempt to discover a conduction anomaly. It was soon apparent that this patient had an alternate cardiac mechanism (Fig. 2*B*) in which the P-R interval was shorter (0.12 to 0.13 second) and the QRS complexes wider (0.10 to 0.11 second) than in periods with normal conduction. Neither mechanism appeared to be dominant, as repeated tracings at frequent intervals showed first one rhythm and then the other. One such spontaneous change in the conduction pathway is illustrated in Fig. 3. Simple experimentation then disclosed that a single dose (1 Gm.) of procaine amide by mouth would eliminate the aberrant conduction for about twelve hours.

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DISCUSSION

This case, although similar to the Wolff-Parkinson-White syndrome, cannot be considered classical. The repeated bouts of tachycardia and the apparent aberrant conduction mechanism with shortened P-R and lengthened QRS are certainly suggestive. However, the P-R interval (0.12 to 0.13 second) is distinctly longer and the QRS (0.10 to 0.11 second) is shorter than is observed in the classical Wolff-Parkinson-White syndrome.

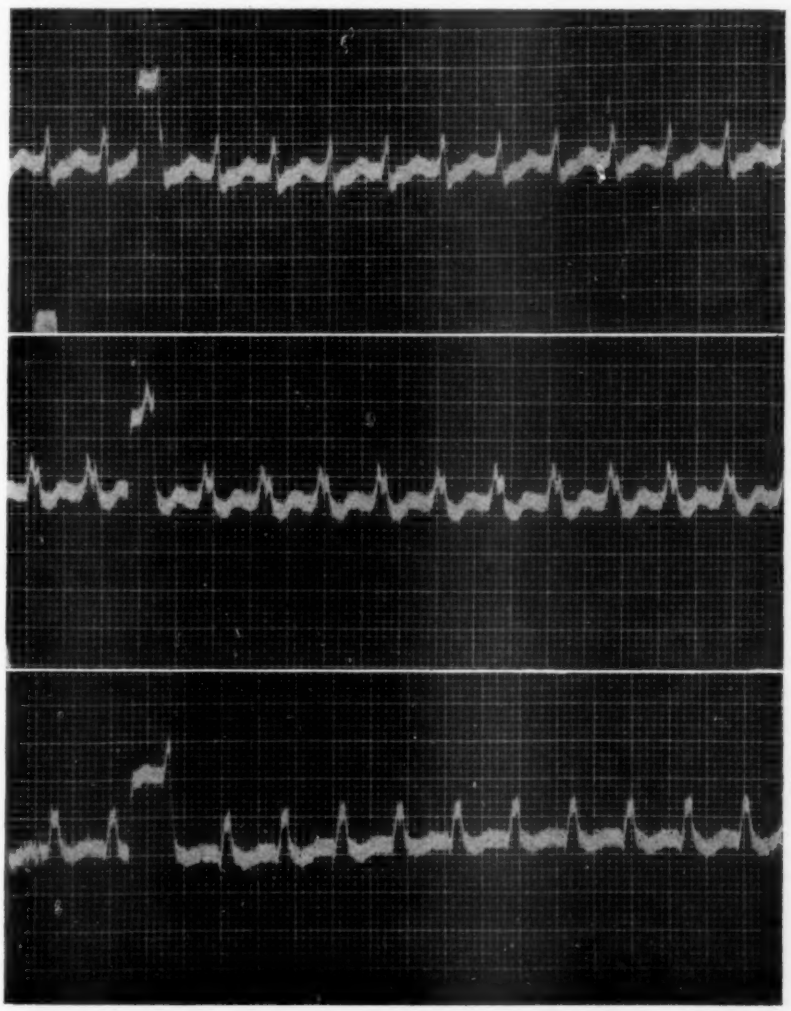

Fig. 1.—The electrocardiogram on admission, demonstrating a nodal tachycardia of 188 per minute. Retrograde P waves are seen in Lead I.

According to Osborne and associates,[1] approximately two-thirds of the normal auriculoventricular conduction time is attributable to delay in the atrioventricular node, particularly its auricular portion. It is therefore tempting to

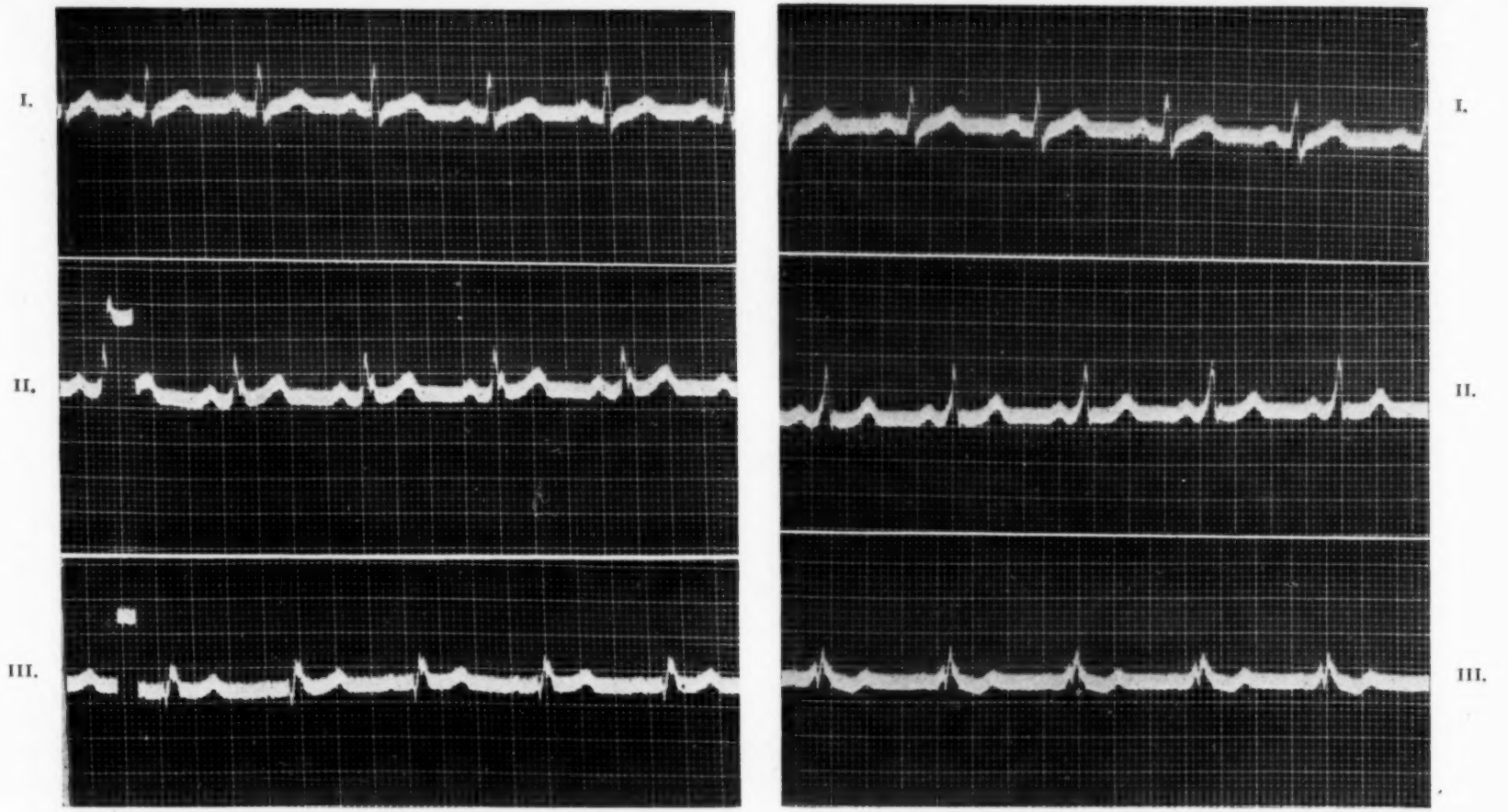

Fig. 2—*A*, Electrocardiogram showing normal sinus rhythm and normal atrioventricular conduction following a single dose (1 Gm.) of procaine amide by mouth. P-R, 0.16 second; QRS, 0.08 second.

B, Electrocardiogram illustrating the aberrant pathway. P-R, 0.12 to 0.13 second; QRS, 0.10 to 0.11 second. The initial portion of QRS is isoelectric in Lead I, and the P-R interval accordingly appears longer than in the other leads.

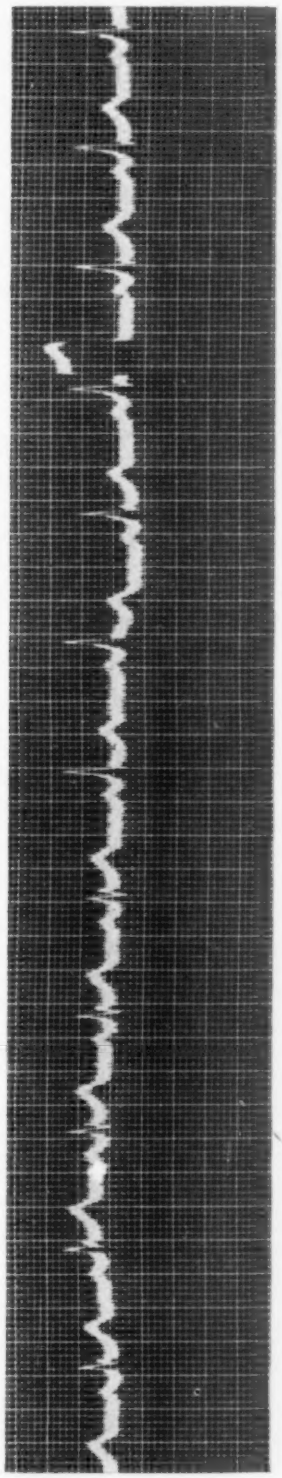

Fig. 3.—Lead II, showing a spontaneous transition from normal to aberrant conduction.

assume that an alternate pathway in this case bypasses part, but not all, of the atrioventricular node. This would account for the somewhat shortened P-R interval and the nodal, rather than ventricular, character of the QRS complexes recorded during aberrant conduction.

Several investigators have reported on the therapy of cardiac arrhythmias with procaine amide.[2-4] Nodal tachycardia, which our case presented, is highly sensitive to this drug. There seems to be little data in the literature, however, concerning the effect of procaine amide on the aberrant conduction of the Wolff-Parkinson-White syndrome. Oral doses markedly inhibited the alternate pathway in this case; single doses of 1 Gm. were followed on two occasions by normal conduction for about twelve hours. The presenting paroxysm of nodal tachycardia was effectively treated with 1 Gm. of procaine amide by mouth. These findings suggest that administration of the drug at twelve-hour intervals would provide effective prophylaxis against abnormal atrioventricular conduction and paroxysmal nodal tachycardia in this case.

SUMMARY

1. Recurrent paroxysmal tachycardia occurred in a patient with intermittent aberrant atrioventricular conduction.

2. A pathway bypassing part, but not all, of the atrioventricular node is suggested as an explanation for the somewhat shortened P-R interval and the somewhat lengthened QRS.

3. Both the presenting nodal tachycardia and the aberrant conduction mechanism were easily controlled by oral procaine amide.

We wish to acknowledge the technical assistance of Corporal Paul Mikkelsen.

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CONGENITAL MALFORMATION OF THE HEART IN ONE OF IDENTICAL TWINS

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ONLY THREE case reports of the presence of congenital heart disease in one of identical twins[4,9,11] have appeared in the literature in the past twenty-five years despite the widespread interest in congenital heart disease. The purpose of this communication is to report a fourth such case.

CASE REPORT

D.K., a 10-year-old white identical boy twin, was first seen in May, 1951, with a chief complaint of pain in his left knee. He was born following a normal full-term monochorionic pregnancy. His mother denied the occurrence of any exanthemata during the pregnancy, nor was there any history of a familial tendency to congenital defects. The patient walked at 9 months and developed normally. He complained of pain in his legs at the age of 3, but his mother denied the occurrence of epistaxis, right upper quadrant pain, or swollen and inflamed joints. She further stated that the patient never had any symptoms referable to the cardiovascular system but did tire more rapidly than other children his age. History by systems revealed that the patient had frequent sore throats prior to a tonsillectomy in 1950. The social and family history was noncontributory.

Physical examination revealed the patient to be a well-developed and well-nourished white boy not acutely ill. The abnormal findings were limited to the cardiovascular system. The cardiac rate and rhythm were normal. The cardiac apex was within the midclavicular line in the fifth intercostal space. P^2 was loud and booming. A harsh systolic murmur and thrill were present in the second left intercostal space at the left sternal border and the murmur was well transmitted to the left but not into the great vessels of the neck. There was no diastolic component. The blood pressure was 118/72 mm. Hg at rest and 118/82 mm. Hg following exercise. The blood pressure in the legs was 158/110 mm. Hg. There was no cyanosis or clubbing of the fingers. No joint pathology was found.

X-ray examination and fluoroscopy in the posteroanterior, right and left anterior oblique positions demonstrated right ventricular hypertrophy, a prominent left pulmonary artery segment with marked pulsations, and normal lung markings without a hilar dance (Fig. 1). A twelve-lead electrocardiogram (Fig. 2) was interpreted as showing right auricular and ventricular hypertrophy with wide swinging QRS complexes of the congenital type.

The final impression was congenital heart disease with an auricular septal defect.

The twin brother's physical examination and roentgenogram (Fig. 3) were entirely normal. He refused an electrocardiogram.

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DISCUSSION

Debreuil-Chambardel[4] in 1927 reported the occurrence of dextrocardia with situs inversus in one of identical twins. In 1945 McClintock[11] observed a patent ductus arteriosus and in 1948 Jeune and Confavreux[9] discussed the presence of situs inversus and cyanosis in one of identical twins. Other investigators[2,5,6,12,13,16] observed the presence of congenital heart disease in both of identical twins. A thorough review of the literature, however, fails to reveal a case similar to the one reported in this paper.

Fig. 1.

Numerous theories have been advanced attempting to explain the etiology of congenital heart disease. The most widely accepted of these is that arrest of development occurs between the fifth and eighth week of intrauterine life during which period the most rapid growth of the cardiac septa and the most complex rotation of the cardiac chambers and great vessels takes place. The etiologies of this are usually divided into intrinsic and extrinsic causes.[5,15]

The most widely accepted intrinsic cause is felt to be due to inherent weakness of the genes.[5,15,18] Several investigators have advanced the theory that lead poisoning in the parents may contribute to the etiology of congenital heart disease in their offspring.[3,5,8]

Many extrinsic causes have been suggested to explain the occurrence of congenital heart disease. Most widely publicized of these is the presence of a viral disease, such as rubella, in the mother during the first trimester of the pregnancy.[5,7,14,15] Warkany[19] suggested that vitamin deficiencies may play a role

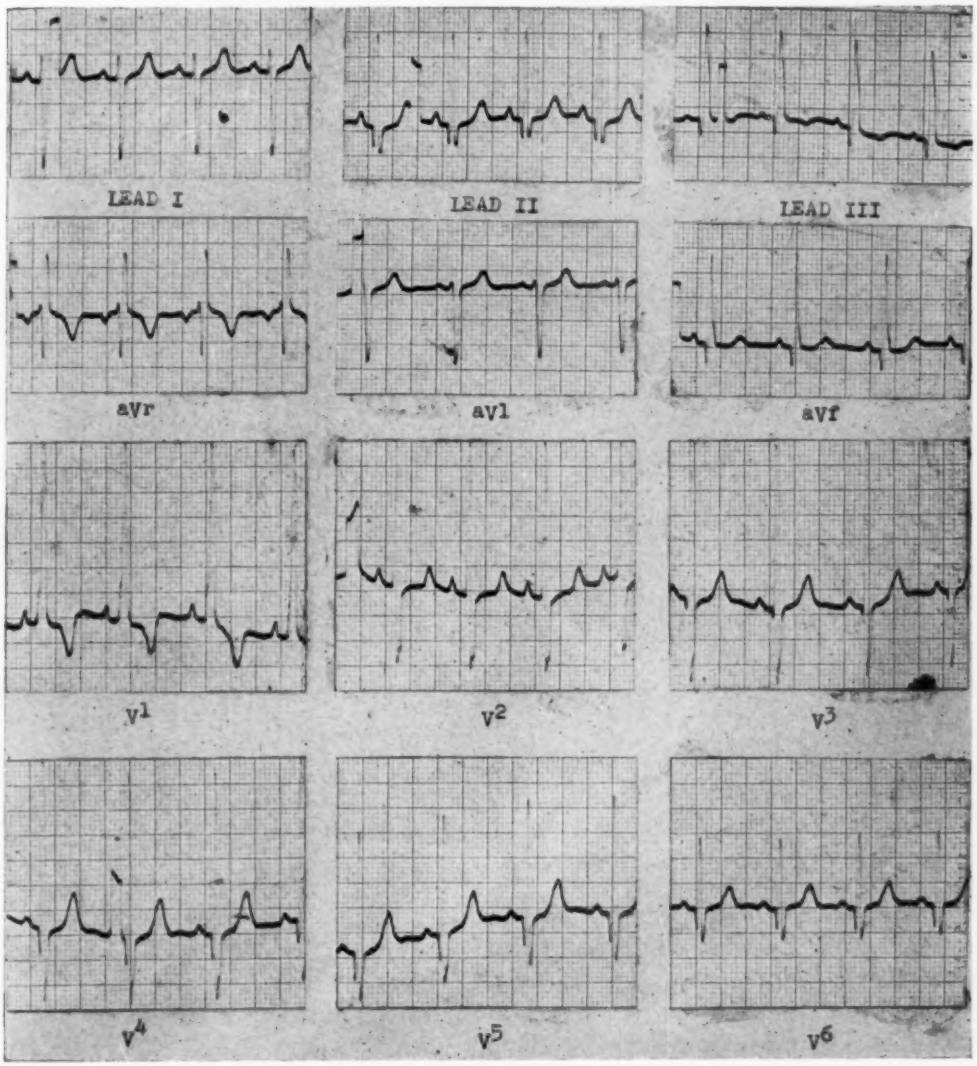

Fig. 2.—Electrocardiogram of D. K., taken Jan. 27, 1951.

in the etiology. Taussig[15] states that abnormalities of the maternal spine may alter the stress on the embryonic vascular bed to such an extent as to cause anomalies in the development of the heart or great vessels. Several workers[1,10,17] have attempted to prove that fetal myocarditis can cause congenital heart disease, but Taussig[15] states that this is the exception, not the rule. However, none of these theories satisfactorily explains the etiology of the congenital defect

present in the case described in this paper in that some indeterminate factor produced a congenital cardiac defect in only one of identical twins.

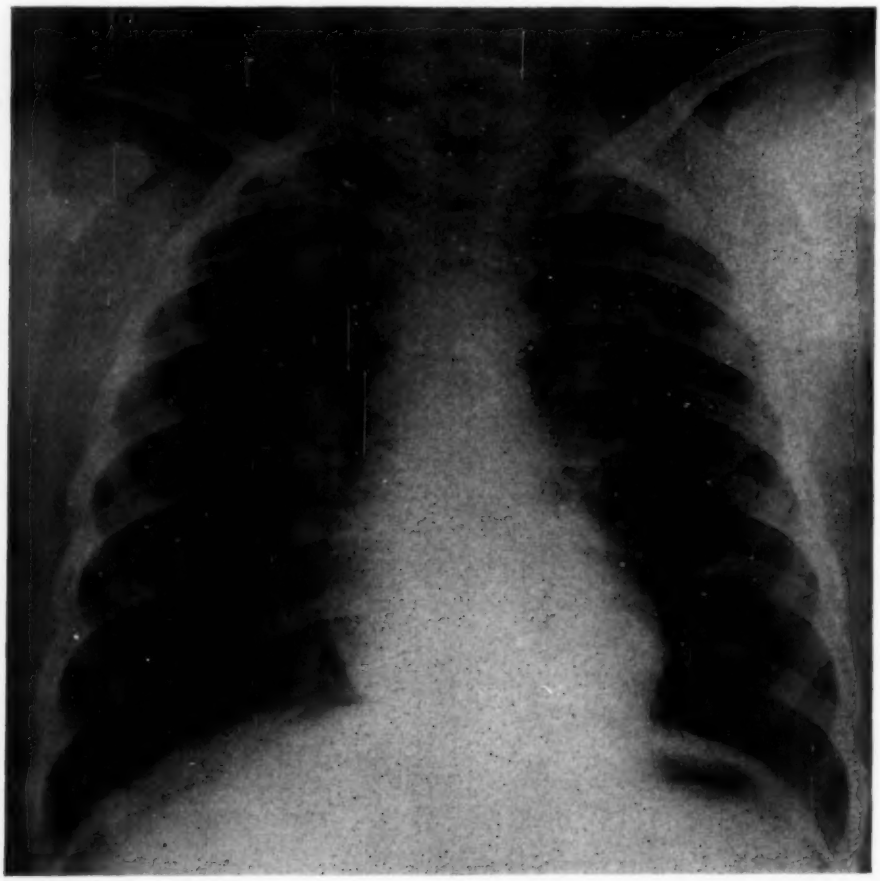

Fig. 3.

SUMMARY

1. A case of congenital heart disease occurring in only one of identical twins has been presented.

2. The literature has been reviewed and the etiology of congenital heart disease has been briefly discussed.

This case was studied through the courtesy of E. M. Mohler, M.D., Senath, Mo.

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Book Reviews

MODERN PRECORDIAL AND EXTREMITY LEADS IN PRACTICE. (DIE NEUZEITLICHEN BRUSTWAND- UND EXTREMITATEN—ABLUTEIGEN IN DER PRAXIS.) By Herbert Reindell, Helmuth Klepzig, and Ludwig Heilmeyer. Stuttgart, 1951, Georg Thieme, Verlag, 179 pages, 64 illustrations. Price DM 22.50.

This practical book, the German equivalent of the smaller monographs in English on the chest and extremity leads of the electrocardiogram, has its own particular "personality." Adequate attention is devoted to the story of the evolution as well as to the description of each new departure in the development of clinical electrocardiography. The documentation includes references to European and American literature; the bibliography, though not large, shows evidence of careful selection. A rather extended discussion of electrocardiograms in 100 normal subjects compared with those in forty trained athletes adds something which would not be found in other books of this type. Evidence is presented which indicates that as the result of athletic training the amplitude of the QRS complexes in the chest leads, especially V_2 and V_4, is increased. Further confirmation of these data could come from making such observations in the same subjects, before, during, and after athletic training. The plan of the book is logical and the book is readable. The illustrations have been carefully mounted but many of the electrocardiograms show 60-cycle current interference. The diagrams are well conceived. For the English-speaking, German-reading student this book offers much that is not found in English books on electrocardiography.

H.S.

MEDICAL RESEARCH COUNCIL, SPECIAL REPORT SERIES, NO. 277. OBSERVATIONS ON THE GENERAL EFFECTS OF INJURY IN MAN. WITH SPECIAL REFERENCE TO WOUND SHOCK. By R. T. Grant and E. B. Reeve. London, England, 1951, H. M. Stationery Office.

This work is a meticulous compilation of data on patients who sustained severe injuries as a result of enemy action during air raids over the London area.

The first part describes injuries to limbs, with extensive statistical treatment regarding the extent of the injury and progress of the shocked patient before, during, and after operation. The authors give a rough means of estimating blood loss when a patient is first seen, based on blood pressure and the extent of the wound. Transfusion and resuscitation can be started on the strength of this before other data are available.

The second portion dealing with abdominal wounds includes studies on postoperative infection, fluid, and electrolyte balance. Both sections deal with different aspects and follow each specific point with illustrative case histories.

In the third section, under "Discussion," the authors give an extensive coverage of the literature on shock, again illustrating the confusion on the shocked state and the difficulty in stating a definition.

Under "Clinical Pathology" methods of estimating blood volume and hemorrhage are discussed in detail, with most of the arguments for and against the methods. Various transfusion fluids are considered and the volume required for various grades of injuries. Hematologic changes due to injuries are listed with the changes produced by transfusion. Disturbances in nitrogen metabolism and water and salt balance are covered.

This is a most extensive compilation of correlated clinical and laboratory data dealing with traumatic wounds. It is not easy reading but contains a wealth of material for those interested in the problem of traumatic shock and treatment of the severely injured.

D.R.W.